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A Prospective Single-Center Study on Electronically Monitored Medication Non-Adherence, Psychosocial Risk Factors and Lifestyle Behaviors after Heart Transplantation – A Study Protocol

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A Prospective Single-Center Study on Electronically Monitored Medication Non-Adherence, Psychosocial Risk Factors and Lifestyle Behaviors after Heart Transplantation – A Study Protocol

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Abstract

Introduction In heart transplant recipients (HTRs), non-adherence (NA) to immunosuppressive (IS) medication and to recommended lifestyle behaviors are a common phenomenon and associated with higher risk of allograft rejection, organ loss, and mortality. Risk factors for NA are highly diverse and still insufficiently researched. Precise measures of NA and an accurate understanding of its etiology are of undisputable importance to detect patients at risk and intervene accordingly. The aim of this study is to assess the accuracy and concordance of different measures for NA as well as to determine potential risk factors.

Methods and Analysis: This is a single-center prospective observational trial. HTRs who are at least aged 18, are no less than 6 months post-transplant and receive Tacrolimus (Prograf[®] or Advagraf[®]), Cyclosporine (Sandimmun[®]), or Everolimus (Certican[®]) as their prescribed IS medication are eligible for participation. At study enrollment, we assess depression, health related quality of life, self-efficacy, social support, attachment, experiences and attitudes towards immunosuppressive medication, emotional responses after transplantation, satisfaction with information about IS medication, and perceptions and beliefs about medications. We further ask patients to rate their lifestyle behaviors concerning alcohol, smoking, diet, physical activity, sun protection, and appointment keeping via questionnaires. Three different measurement methods for NA are applied at T0: self-reports, physician's estimates, and IS trough levels. NA is monitored prospectively using an electronic

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3 27 multicompartment pillbox (MEMS, VAICA©) over a 3-month period. Meanwhile, participants receive phone
4 28 calls every second week to obtain additional self-reports, resulting in a total of 7 measurement points.
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6
7 29 **Ethics and Dissemination:** The study was approved by the Clinical Ethics Committee of the University
8
9 30 Hospital Erlangen (Friedrich-Alexander-University, Erlangen-Nürnberg). Written informed consent is
10 31 attained from all participants. The results of this study will be published in peer-reviewed journals
11 32 and presented at conferences.
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15
16 33 **Keywords:** heart transplantation, electronic monitoring, self-reports, trough level variability, adherence,
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18 34 psychosocial factors, lifestyle behavior, non-pharmacological adherence, prospective study, study protocol
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22 35 Article Summary
23
24
25 36 Strengths and Limitations of this study
26
27
28 37 • This is the first study assessing potential risk factors of immunosuppressive NA and non-
29 38 pharmacological NA by prospectively applying electronic monitoring in heart transplant
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31 39 recipients
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35 40 • This study combines different measurement methods for NA, such as electronic monitoring, self-
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37 41 reports, physician's estimates, and IS trough level variability
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39 42 • One limitation of our study is a potential initial intervention effect induced by electronic
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41 43 monitoring; however, adherence behavior is likely to stabilize after app. 40 days
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44 44 • This is a single-center study with a moderate sample size
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47 45 **Trial registration number:** DRKS00020496
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49 46 Word count: 2325
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53 47 **Introduction**
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55
56 48 Adherence is defined as "the process by which patients take their medication as prescribed" [1].
57
58 49 Especially in transplant recipients, regular and accurate intake of immunosuppressants is vital for
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60 50 organ survival [2, 3]. Immunosuppressive non-adherence (NA) rates in transplant recipients differ

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3 51 greatly depending on the respective organ, with a mean prevalence of 22.6% of patients per year [4-
4 52 6]. For heart transplant recipients (HTRs), NA rates range between 4.6% and 39.2% [4-8]. Due to a
5 53 rising awareness of its detrimental impact on allograft rejection, organ loss, and mortality [2, 9],
6 54 research on NA in HTRs has increased substantially in recent years. Already minor deviations from
7 55 the medical regimen have been associated with hazardous effects on organ and patient survival [10].
8 56 Various assessment tools for NA are currently available, comprising both indirect and direct
9 57 measures. Direct measures include direct observation and blood assays, whereas for indirect
10 58 measures pill counts, self-reports, collateral reports, and electronic monitoring are used [11, 12]. The
11 59 most frequently employed NA measure for HTRs is self-report [12]. Despite their susceptibility to
12 60 errors, self-reports are considered practical and inexpensive tools for NA assessment [11, 13].
13 61 Although electronic monitoring allows insights into patterns of adherence behavior, its use can be
14 62 quite expensive and labor-intensive [11, 13] and thus is only very sparsely used in HTRs [12]. Blood
15 63 assays such as the trough level variability are also frequently applied as an adherence measure, since
16 64 they have increasingly been associated with rejection and mortality in HTRs [9, 14, 15]. Collateral
17 65 reports, however, are mostly considered unreliable measurement methods for NA [16]. Few studies
18 66 have examined the accuracy and concordance of these NA measures; especially in HTRs, research is
19 67 scarce. However, an accurate assessment of NA seems crucial in order to detect patients at risk and
20 68 to intervene accordingly.

21 69 Besides the relevancy of immunosuppressant intake, certain lifestyle habits can also adversely affect
22 70 organ survival as well as patient morbidity and mortality after transplantation [17-20]. Nonetheless, a
23 71 considerable amount of HTRs insufficiently adheres to certain lifestyle recommendations. Compared
24 72 to other types of organs, HTRs display particularly high NA rates for physical exercise, with
25 73 prevalences ranging between 33.7% and 49.1% [4, 7, 17, 21]. For following dietary
26 74 recommendations, NA rates between 22.9% and 46% were observed, while those for keeping follow-
27 75 up appointments varied between 5.7% and 37.3% [4, 7, 17, 18, 21]. Alcohol use was found for app.
28 76 4.9% to 27.8% of HTRs, while tobacco use was confirmed by 3.2% to 9.1% [4, 7, 17, 21]. Helmy et al.
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3 77 [17] further revealed that up to 39.9% of HTRs did not apply sun protection as recommended.
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5 78 Correlations between the various domains of lifestyle habits could not be detected [7], whereas
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7 79 immunosuppressive NA was found to be interrelated with appointment keeping [18] and smoking
8
9 80 [8]. Research on non-pharmacological NA is sparse and only few have examined the occurrence of
10
11 81 and interrelations between various NA areas. Thus far, there are no studies connecting non-
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13 82 pharmacological NA with electronically monitored immunosuppressive NA in HTRs.
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16 83 Risk factors for NA are highly diverse and multifactorial. Depression [22], lower social support [4, 6, 7,
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18 84 23], lower quality of life [21], non-white ethnicity [4, 9], negative feelings [24, 25], attitudes to
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20 85 medication or treatment [25-27], higher frequency of medication intake [28], longer time since
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22 86 transplantation [6, 24, 26], and younger age [24] have recently been associated with NA in studies
23
24 87 that comprised HTRs. In renal transplant recipients, anxiety [29], male sex [29, 30], lower self-efficacy
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26 88 [31-33], and avoidant attachment [34] were also found to be linked to increased NA. Although a
27
28 89 considerable amount of research is devoted to the reasons and risk factors for immunosuppressive
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30 90 NA, there is still a wide array of contradictory and heterogeneous results. Further, research
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32 91 examining risk factors exclusively in HTRs is sparse. Most studies examining risk factors for NA use
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34 92 self-reports, physicians' estimates, or trough levels. To our knowledge, no study has examined
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36 93 potential risk factors for NA in HTRs that were measured by applying electronic monitoring. What is
37
38 94 more, studies on risk factors for NA to recommended lifestyle behaviors are missing. In order to
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40 95 develop adequate adherence interventions, assessing the accuracy of NA measures as well as
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42 96 determining factors that promote NA is of paramount importance. With this study, we cover relevant
43
44 97 topics on adherence after heart transplantation and wish to fill substantial gaps in current research.
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52 98 **Study Aims**

53
54 99 The aim of our study is to investigate electronically monitored non-adherence in heart transplant
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56 100 recipients over a period of 3 months during the phase of medication implementation [1, 35]. The
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58 101 following three issues will be addressed:
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3 102 1) Measurement Methods: Do different measurement methods of NA correlate with each other
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5 103 at the beginning of the study? Does electronically monitored NA coincide with self-reported
6
7 104 NA during the course of the study?
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10 105 2) Psychosocial Predictors: Can certain psychosocial factors predict electronically monitored NA
11
12 106 in HTRs?
13
14 107 3) Non-pharmacological adherence and Lifestyle Behaviors: To what extend do heart transplant
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16 108 recipients comply with lifestyle requirements? Does immunosuppressive medication coincide
17
18 109 with healthy lifestyle behaviors? What are potential risk factors for these behaviors?
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23 110 **Methods and Analysis**

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25 111 **Setting and Recruitment**

26
27 112 This work is part of the APT (Adherence and Psychological Health after Transplantation) research
28
29 113 project of the Department of Psychosomatic Medicine and Psychotherapy and takes place in
30
31 114 cooperation with the Department of Cardiac Surgery and the Department of Nephrology and
32
33 115 Hypertension in Erlangen. This sub-study is conducted at the outpatient clinic of the Department of
34
35 116 Cardiac Surgery of the University Hospital of Erlangen. During the course of one year, the sample is
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37 117 consecutively derived from heart transplant recipients undergoing their routine follow-up
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39 118 examination. Prior to their appointment, eligible patients are contacted via telephone and receive
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41 119 study information and questionnaires by mail, if interested.
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48 120 **Study Population**

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50 121 Inclusion criteria for the study are patients who are at least 18 years old, have undergone heart
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52 122 transplantation at least six months ago, and receive either Tacrolimus (Advagraf[®] or Prograf[®]),
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54 123 Cyclosporine (Sandimmun[®]) or Everolimus (Certican[®]) as their prescribed immunosuppressive
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56 124 medication. Patients with neurocognitive disabilities, who have no sufficient knowledge of the
57
58 125 German language, and/or have severe mental disorders, will be excluded from the study. We
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3 126 specifically focus on medication implementation and exclude cases of initiation [1, 35]. Of app. 100
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5 127 eligible patients per year, we expect a responder rate of app. 50%, resulting in a potential sample of
6
7 128 50 heart transplant recipients. We attain written informed consent from all participating patients.
8
9
10 129 The study was approved by the Clinical Ethics Committee of the University Hospital Erlangen
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12 130 (Friedrich-Alexander-University, Erlangen-Nürnberg, FAU).
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131 **Measurement Methods**

132 **Immunosuppressive Adherence Measures**

133 ***Collateral Report***

134 Adherence assessments are made after the patients' appointments with their treating physician. The
135 respective cardiologist is asked to rate the patients' IS adherence both on a 5-Point Likert Scale
136 (1=very good, 5=very bad) and on a 10cm (0-100%) Visual Analogue Scale (VAS).

137 ***Self-report***

138 In order to assess self-reported NA, the patients equally receive a 10cm (0-100%) Visual Analogue
139 Scale (VAS, part of the BAASIS© [36] Interview). We further apply the Basel Assessment of
140 Adherence to Immunosuppressive Medication Scale (BAASIS© Questionnaire [36]), which consists of
141 four items that relate to the medication taking behavior of the last 4 weeks. It assesses four types of
142 IS non-adherence (dose taking, drug holiday, timing adherence >2h, and dose reduction) that can be
143 rated on a 6-point scale (0=never/5=every day). Patients who consent to at least one of these four
144 items are classified as non-adherent. We added a further question on timing adherence covering an
145 additional intake interval of ±30min. During the course of the study, we also ask for the absolute
146 frequency of IS intake deviations since the last phone call (recall period of app. 2 weeks).

147 ***Subtherapeutic trough levels***

148 IS levels are routinely checked at each follow-up examination. We will use the IS trough level that is
149 measured at study enrollment as well as up to three antecedent measures [37], since reliability
150 improves with an increased number of measurements points [16, 38]. IS levels will be standardized

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3 151 by their respective target levels which can be changed individually by the treating cardiologist
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5 152 depending on the clinical results. We then will assess IS trough level variability (CV) that has been
6
7 153 associated with graft rejection, mortality, and NA [14, 15, 39].
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10 154 **Electronic Monitoring**
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12 155 Electronic monitoring of NA is taking place with a multicompartiment pillbox (VAICA SimpleMed©)
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14 156 which provides medication storage for 7 days with up to 4 doses per day. Medication extraction is
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16 157 automatically recorded and transferred to a web portal where the individual immunosuppressive
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18 158 medication schedules of each patient are registered. For timing adherence we set intervals at
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20 159 ±30minutes and ±2hours. Reminder functions (visual/acoustic signals) are disabled to keep a possible
21
22 160 intervention effect at a minimum. In addition, participants are requested to keep a diary for
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24 161 incidence where IS extraction does not coincide with IS intake or the medication is taken from
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26 162 another source (pocket, take-away box, etc.).
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31 163 **Psychosocial Variables**
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33 164 For the assessment of potential psychosocial predictors of NA, each patient is asked to fill in a
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35 165 questionnaire battery at the beginning of the study. The applied measures are depicted in table 1.
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39 166 **Table 1 Psychosocial Constructs and applied questionnaires**
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41 Psychosocial Construct	42 Instrument	43 Information
44 Depression	45 PHQ-9 [40, 41]	46 Self-report screening instrument of depression, 9 Items, 4-point scale
47 Perceived Social Support	48 FSozU-7 [42]	49 Self-report instrument on social support (practical support, emotional support, social integration), Short form of F-SozU, 7 items, 5-point scale
50 Perceived health related Quality of Life	51 WHOQoL-BREF [43]	52 Self-report instrument on perceived health related quality of life (physical health, psychological health, social relationships, environment), short from of WHOQoL-100, 26 items, 5-point scale
53 Self-Efficacy	54 SWE [44, 45]	55 Self-report questionnaire, 10 Items, 4-point scale
56 Attachment	57 RSQ [46, 47]	58 Self-report questionnaire , 30 Items, 5-point scale
59 Subjective experiences and attitudes towards immunosuppressive medication	60 MESI [48]	61 Self-report questionnaire, 7 Items, 5-point scale
62 Emotional Responses after Organ Transplantation	63 TxEQ [49, 50]	64 Self-report questionnaire on emotional responses after Tx (guilt, worry, disclosure, adherence, responsibility), 23 Items, 5-point scale

Satisfaction with Information about immunosuppressive medication	SIMS-D [51, 52]	Self-report questionnaire, 17 Items, 5-point scale
Perceptions of and Beliefs about medications	BMQ [53, 54]	Self-report questionnaire, 18 items, 5-point scale

167 Non-pharmacological Non-Adherence and lifestyle behavior

168 To assess non-pharmacological NA to recommended lifestyle behaviors we use self-report data on
 169 physical activity, diet, sun protection, smoking, appointment keeping, and alcohol use. For better
 170 comparability, we apply similar measurement methods used in previous research [17]. How each
 171 component is measured can be viewed in table 2.

172 **Table 2 Methods to assess non-pharmacological NA to recommended lifestyle behaviors**

Variable	Instrument	Information
Physical Activity	Brief Physical Activity Assessment tool [55]	2 items, frequency of intense and moderate physical activity during an average week (Adherent: sufficiently active, Non-adherent: insufficiently active)
Smoking	Self-developed (based on measure used by Helmy et al.[17])	1 Item on current smoking status, Adherent: Never Smoked/stopped before Htx, Non-Adherent: stopped after Htx, Smokes sometimes/several times a week/daily)
Alcohol use	Self-developed (based on measure used by Helmy et al.[17])	2 Items on current alcohol use (frequency of alcohol use per average week, usual quantity of alcohol intake), Non-Adherent: >1 drink/day (0.33l) (women), >2 drinks/d (men)
Sun protection	According to measure developed by Helmy et al.[17]	4 Items on current sun protection (using sun screen, wearing protective clothing, staying in the shade, being sensitive to the time of day), 5-point scale, Adherent: always using ≥1 of protection methods, Non-Adherent: not always using at least 1
Diet	According to measure developed by Helmy et al.[17]	1 items on adherence to general dietary recommendations, 4 items on daily diet (sugar, low calorie, low saturated fats, low salt), 5-point scale, Adherent: min. score 4-5 on all dietary recommendation, Non-Adherent: scores of 1-3 on any scale
Appointment Keeping	Self-developed (based on measure used by Helmy et al.[17])	1 Item, frequency of unexcused absence at scheduled follow-up appointments since transplantation (Adherent: 0, Non-Adherent: ≥1)

Note: HTx = Heart Transplantation.

173 **Study Design and Measurement Points**

174 This is a prospective clinical observational trial. Electronic monitoring will take place for three
175 months. Meanwhile, each participant will receive phone calls in an interval of two weeks. Self-reports
176 on potential incidents of NA referring to the last two weeks will be obtained. At the end of the study,
177 patients will receive a feedback on their medication intake behavior. The timeline of our study
178 procedure can be viewed in figure 1.

179 Figure 1

180 **Patient and Public Involvement**

181 Patients and the public are not involved in the design, recruitment, and conduction of this study.

182 **Statistical Analysis Plan**

183 Data will be analyzed using SPSS 21 for Microsoft Windows© and the nlme-package [56] and the
184 lme4-package [57] for R version 3.5.1. For descriptive statistics we will depict frequencies, mean
185 values, standard deviations, and ranges. For group comparisons (Non-Responder-Analyses) we will
186 use independent T-tests, Mann-Whitney-U-tests, and Chi²-tests. Cohen's kappa and the Intraclass
187 Correlation Coefficient (ICC) will be used to conduct analyses on the association of measurement
188 methods. For prospective analyses, we will perform linear regressions with electronic monitoring as
189 the outcome variable. To assess changes in probability of adherence over time, two alternative linear
190 mixed models (strictly linear and piecewise linear) will be conducted. Results will be interpreted on a
191 significance level of p < .05.

192 **Progress**

193 Recruitment started in September 2019. Of 31 eligible patients, 24 could be contacted via telephone
194 before their follow-up examination. Of those, 13 (54.17%) agreed to participate and are currently
195 taking part in our study, whereas 11 declined participation. Reasons for refusal are lack of study
196 interest, lack of time, sickness, and inconvenience or impossibility of integration of the pillbox into

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3 197 daily routine. Sociodemographic and biomedical data of all patients already included in our study are
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5 198 depicted in table 3.
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11 199 **Table 3 Sociodemographic and biomedical data of current participants**

		Patients (N =13)
Age (M, SD, range)		58.36 (± 15.4), 32-82
Sex (n, %)	Males	13 (100)
	Females	0 (0)
Marital Status (n, %)	Single	3 (23.08)
	Married/in a relationship	7 (53.85)
	Separated/Divorced	1 (7.69)
	No information	2 (15.38)
Immunosuppressive Medication (n, %)	Advagraf \circledR (once daily)	0 (0)
	Prograf \circledR (twice daily)	7 (52.85)
	Sandimmun \circledR (twice daily)	3 (23.08)
	Certican \circledR	1 (7.69)
	Combination of Certican \circledR and Prograf \circledR /Sandimmun \circledR	2 (15.38)
Last transplantation (Median, SD, range)		2013 (± 5.24), 2003-2017

200 Discussion

201 To our knowledge, this is the first study assessing potential risk factors of immunosuppressive NA
202 and non-pharmacological NA by prospectively applying electronic monitoring as the main NA
203 measure. To date, no study has combined electronic monitoring, self-reports, physicians' estimates,
204 and IS trough level variability to measure NA in HTRs. Although, measuring NA might induce an
205 intervention effect resulting in temporarily improved adherence, adherence behavior is likely to
206 stabilize to its base level after app. 35-40 days [58, 59]. Yet, by applying a combination of NA
207 measures, especially electronic monitoring, more accurate statements about prevalences of NA and
208 its potential risk factors in HTRs can be made. Precise measures and a detailed knowledge of
209 potential determinants are crucial in order to develop adequate adherence interventions and reduce
210 the fatal consequences of NA. In recent years, several well designed interventions for the
211 improvement of immunosuppressive adherence have been published [60-64]. Most of these
212 interventions are tailored to meet needs of renal transplant recipients. Interventions specifically for

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3 213 HTRs are sparse or non-existent, especially since research on prevalences and risk factors of NA are
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5 214 mostly focused on renal transplant recipients [4].
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7 215 Further, more research on lifestyle behaviors is required to fully understand its reasons as well as
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9 216 potential implications on rejection and organ survival in HTRs. The potentially harmful consequences
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11 217 of insufficient physical activity, inadequate sun protection, tobacco and alcohol use, and unhealthy
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13 218 diet are already well-established in healthy populations [65-69]. But especially HTRs who are obliged
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15 219 to life-long IS intake are at an even greater risk of developing chronic diseases and health issues
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17 220 when engaging in unhealthy lifestyle behaviors [17, 70, 71]. In order to prevent comorbid diseases
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19 221 and health damages, the development of interventions specifically targeting lifestyle habits are
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21 222 substantial. Two recent studies on renal transplant recipients showed an improvement of sun-
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23 223 protective behavior after an educational intervention [72-74]. Interventions for the improvement of
24
25 224 other lifestyle behaviors are lacking. For the development of adequate lifestyle interventions, the
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27 225 investigation of reasons and risk factors for these unhealthy behaviors is a prerequisite that we wish
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29 226 to meet with this study.

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31 227 If patients with acute forms of severe depression, excessive substance abuse or other self-harming
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33 228 behaviors are detected during study recruitment, immediate interventions or transfers to the
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35 229 respective outpatient clinics can be initiated.

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37 230 With the combination of lifestyle habits, psychosocial factors, and a bandwidth of
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39 231 immunosuppressive NA measures, especially electronic monitoring, our study will provide a
40
41 232 promising opportunity to shed further light onto highly clinically relevant topics. We expect that our
42
43 233 findings will contribute to the refinement of NA measures as well as the development of
44
45 234 comprehensive interventions for HTRs.

54 235 **Ethics and Dissemination**

55
56 236 The study was approved by the Clinical Ethics Committee of the University Hospital Erlangen
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58 237 (Friedrich-Alexander-University, Erlangen-Nürnberg, FAU). Written informed consent is attained from

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3 238 all participants. The results of this study will be published in peer-reviewed journals and presented at
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5 239 national and international conferences.
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11 240 Abbreviations:
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13 241 VAS: Visual Analogue Scale, NA: Non-Adherence, IS: Immunosuppressant/immunosuppressive, HTR: Renal Transplant
14 242 Recipient, HTx: Heart Transplantation, ICC: Intraclass Correlation Coefficient
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16
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18 243 Acknowledgements:
19
20 244 We wish to thank the staff of the Department of Cardiac Surgery at the University Hospital of Erlangen for enabling the
21 organization and conduction of this project. We especially would like to thank all patients who are taking part in our study.
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25 246 Competing Interests
26
27 247 All authors declare that they have no competing interests
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31
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33
34

35 250 Availability of data and material
36
37 251 The data supporting our findings can be requested from Dipl.-Psych. Marietta Lieb (marietta.lieb@uk-erlangen.de) and Prof.
38
39 252 Yesim Erim (yesim.erim@uk-erlangen.de)
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42 253 Author Contributions
43
44 254 ML designed and drafted the manuscript and is currently conducting the study. YE supervises and supports the
45 conceptualization and conduction of the study. MW enabled the initiation of this project and supervises study coordination.
46
47 255 MS supports patient recruitment. All authors (ML, MW, MS, YE) revised the manuscript critically for important intellectual
48 content, have given final approval of the version to be published and agree to be accountable for all aspects of the work in
49
50 256 ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and
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52 257 resolved.
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44 483 Figure titles and legends:
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46 484 Figure 1. Timeline of study procedure. 2w = 2 weeks.
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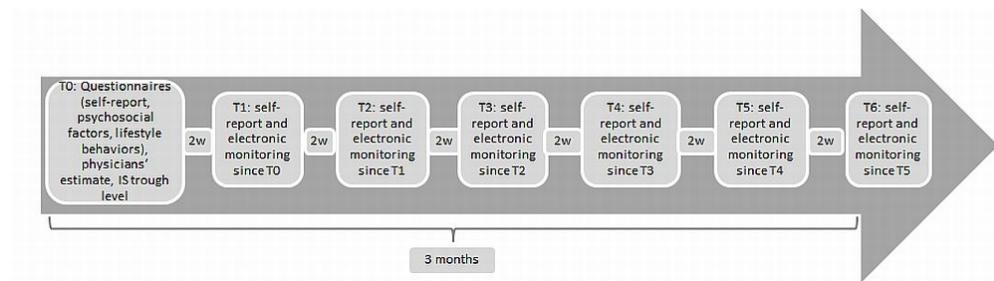


Figure 1. Timeline of study procedure. 2w = 2 weeks.

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A Prospective Single-Center clinical observational Study on Electronically Monitored Medication Non-Adherence, its Psychosocial Risk Factors and Lifestyle Behaviors after Heart Transplantation – A Study Protocol

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Abstract

Introduction In heart transplant recipients (HTRs), non-adherence (NA) to immunosuppressive (IS) medication and to recommended lifestyle behaviors are a common phenomenon and associated with higher risk of allograft rejection, organ loss, and mortality. Risk factors for NA are highly diverse and still insufficiently researched. Precise measures of NA and an accurate understanding of its etiology are of undisputable importance to detect patients at risk and intervene accordingly. The aim of this study is to assess the accuracy and concordance of different measures for NA as well as to determine potential risk factors.

Methods and Analysis: This is a single-center prospective observational trial. HTRs who are at least aged 18, are no less than 6 months post-transplant and receive Tacrolimus (Prograf[®] or Advagraf[®]), Cyclosporine (Sandimmun[®]), or Everolimus (Certican[®]) as their prescribed IS medication are eligible for participation. We only include patients during the phase of medication implementation. At study enrollment, we assess depression, health related quality of life, self-efficacy, social support, attachment, experiences and attitudes towards immunosuppressive medication, emotional responses after transplantation, satisfaction with information about IS medication, and perceptions and beliefs about medications. We further ask patients to rate their lifestyle behaviors concerning alcohol, smoking, diet, physical activity, sun protection, and appointment keeping via questionnaires. Three different measurement methods for NA are applied at T0: self-reports, physician's estimates, and IS trough levels. NA is monitored prospectively using an electronic

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3 28 multicompartment pillbox (MEMS, VAICA©) over a 3-month period. Meanwhile, participants receive phone
4 29 calls every second week to obtain additional self-reports, resulting in a total of 7 measurement points.
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7 30 **Ethics and Dissemination:** The study was approved by the Clinical Ethics Committee of the University
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9 31 Hospital Erlangen (Friedrich-Alexander-University, Erlangen-Nürnberg). Written informed consent is
10 32 attained from all participants. The results of this study will be published in peer-reviewed journals
11 33 and presented at conferences.
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16 34 **Keywords:** heart transplantation, electronic monitoring, self-reports, trough level variability, adherence,
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18 35 psychosocial factors, lifestyle behavior, non-pharmacological adherence, prospective study, study protocol
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23 36 Article Summary
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25 37 Strengths and Limitations of this study
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28 38 • This is the first study assessing potential risk factors of immunosuppressive NA and non-
29 39 pharmacological NA by prospectively applying electronic monitoring in heart transplant
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31 40 recipients
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34 41 • This study combines different measurement methods for NA, such as electronic monitoring, self-
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36 42 reports, physician's estimates, and IS trough level variability
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38 43 • One limitation of our study is a potential initial intervention effect induced by electronic
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40 44 monitoring; however, adherence behavior is likely to stabilize after app. 40 days
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43 45 • This is a single-center study with a moderate sample size
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48 46 Trial registration number: DRKS00020496
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53 48 Introduction

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55 49 Adherence is defined as "the process by which patients take their medication as prescribed" [1].
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57 50 Especially in transplant recipients, regular and accurate intake of immunosuppressants is vital for
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59 51 organ survival [2, 3]. Immunosuppressive non-adherence (NA) rates in transplant recipients differ
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3 52 greatly depending on the respective organ, with a mean prevalence of app. 22.6% of patients per
4 53 year [4-10]. For heart transplant recipients (HTRs), NA rates range between 4.6% and 39.2% [4-7, 11,
5 54 12], influenced by the choice of measurement methods, operational definitions, and case finding
6 55 methods. Due to a rising awareness of its detrimental impact on allograft rejection, organ loss, and
7 56 mortality [2, 13], research on NA in HTRs has increased substantially in recent years. Already minor
8 57 deviations from the medical regimen have been associated with hazardous effects on organ and
9 58 patient survival [14]. Various assessment tools for NA are currently available, comprising both
10 59 indirect and direct measures. Direct measures include direct observation and blood assays, whereas
11 60 for indirect measures pill counts, self-reports, collateral reports, and electronic monitoring are used
12 61 [15, 16]. The most frequently employed NA measure for HTRs is self-report [16]. Despite their
13 62 susceptibility to errors, such as memory bias, social desirability, self-reports are considered practical
14 63 and inexpensive tools for NA assessment [15, 17-20]. Although electronic monitoring allows insights
15 64 into patterns of adherence behavior, its use can be quite expensive and labor-intensive [15, 17].
16 65 Except for few studies [2, 5, 14], electronic monitoring is only very sparsely used in HTRs [16]. Blood
17 66 assays such as the trough level variability are also frequently applied as an adherence measure, since
18 67 they have increasingly been associated with rejection and mortality in HTRs [13, 21, 22]. Collateral
19 68 reports, however, are mostly considered unreliable measurement methods for NA [23]. To increase
20 69 sensitivity, some studies also use a combination of measurement methods to assess NA, which
21 70 mostly results in very high NA rates [5, 15]. Few studies have examined the accuracy and
22 71 concordance of these NA measures [17, 24-28]; especially in HTRs, research is scarce. However, an
23 72 accurate assessment of NA seems crucial in order to detect patients at risk and to intervene
24 73 accordingly.

25 74 Besides the relevancy of immunosuppressant intake, certain lifestyle habits can also adversely affect
26 75 organ survival as well as patient morbidity and mortality after transplantation [29-33]. Nonetheless, a
27 76 considerable amount of HTRs insufficiently adheres to certain lifestyle recommendations. Compared
28 77 to other types of organs, HTRs display particularly high NA rates for physical exercise, with

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3 78 prevalences ranging between 33.7% and 49.1% [4, 11, 29, 34]. For following dietary
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5 79 recommendations, NA rates between 22.9% and 46% were observed, while those for keeping follow-
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7 80 up appointments varied between 5.7% and 37.3% [4, 11, 29, 30, 34]. Alcohol use was found for app.
8
9 81 4.9% to 27.8% of HTRs, while tobacco use was confirmed by 3.2% to 9.1% [4, 11, 29, 34]. Helmy et al.
10
11 82 [29] further revealed that up to 39.9% of HTRs did not apply sun protection as recommended.
12
13 83 Correlations between the various domains of lifestyle habits could not be detected [11], whereas
14
15 84 immunosuppressive NA was found to be interrelated with appointment keeping [30] and smoking
16
17 85 [12]. Research on non-pharmacological NA is sparse and only few have examined the occurrence of
18
19 86 and interrelations between various NA areas. However, research on solid organ transplant recipients
20
21 87 that included HTRs found certain patient-related risk factors for unhealthy lifestyle behaviors. Post-
22
23 88 transplant smoking was found to be more prevalent in men, but less in older patients and those with
24
25 89 comorbid physical diseases such as diabetes and hypertension [33]. Smoking in turn, was found to be
26
27 90 a risk factor for post-transplant at-risk drinking, while post-transplant alcohol use in general could be
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29 91 linked with male gender, being employed, and a history of psychiatric illness, among others [35]. No
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31 92 significant risk factors were found for low physical exercise [36]. Most of these studies are based on
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33 93 results of kidney recipients, whilst research on heart recipients is rare. Especially studies connecting
34
35 94 non-pharmacological NA with electronically monitored immunosuppressive NA in HTRs are missing.
36
37 95 Risk factors for immunosuppressive NA on the other hand are well examined, although highly diverse
38
39 96 and multifactorial. Depression [37], lower social support [4, 6, 11, 38], lower quality of life [34], non-
40
41 97 white ethnicity [4, 13], negative feelings [39, 40], attitudes to medication or treatment [40-42],
42
43 98 higher frequency of medication intake [43], longer time since transplantation [6, 39, 41], and younger
44
45 99 age [39] have recently been associated with NA in studies that comprised HTRs. In renal transplant
46
47 100 recipients, anxiety [44], male sex [44, 45], lower self-efficacy [46-48], and avoidant attachment [49]
48
49 101 were also found to be linked to increased NA. Although a considerable amount of research is devoted
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51 102 to the reasons and risk factors for immunosuppressive NA, there is still a wide array of contradictory
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53 103 and heterogeneous results. Further, research examining risk factors exclusively in HTRs is sparse.
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3 104 Most studies examining risk factors for NA use self-reports, physicians' estimates, or trough levels. To
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5 105 our knowledge, no study has examined potential risk factors for NA in HTRs that were measured by
6
7 106 applying electronic monitoring. What is more, studies on risk factors for NA to recommended
8
9 107 lifestyle behaviors are missing. In order to develop adequate adherence interventions, assessing the
10
11 108 accuracy of NA measures as well as determining factors that promote NA is of paramount
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13 109 importance. With this study, we cover relevant topics on adherence after heart transplantation and
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15 110 wish to fill substantial gaps in current research.
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20 111 **Study Aims**
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23 112 The aim of our study is to investigate electronically monitored non-adherence in heart transplant
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25 113 recipients over a period of 3 months during the phase of medication implementation [1, 50]. The
26
27 114 following three research questions (RQ) will be addressed:
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- 30
31 115 1) Measurement Methods: Do different measurement methods of NA correlate with each other
32
33 116 at the beginning of the study? Does electronically monitored NA coincide with self-reported
34
35 117 NA during the course of the study?
36
37 118 2) Psychosocial Predictors: Can certain psychosocial factors predict electronically monitored NA
38
39 119 in HTRs?
40
41 120 3) Non-pharmacological adherence and Lifestyle Behaviors: To what extend do heart transplant
42
43 121 recipients comply with lifestyle requirements? Does immunosuppressive medication coincide
44
45 122 with healthy lifestyle behaviors? What are potential risk factors for these behaviors?
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51 123 **Methods and Analysis**
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54 124 **Setting and Recruitment**
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57 125 This work is part of the APT (Adherence and Psychological Health after Transplantation) research
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59 126 project of the Department of Psychosomatic Medicine and Psychotherapy and takes place in
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3 127 cooperation with the Department of Cardiac Surgery and the Department of Nephrology and
4
5 128 Hypertension in Erlangen. This sub-study is conducted at the outpatient clinic of the Department of
6
7 129 Cardiac Surgery of the University Hospital of Erlangen. During the course of one year, the sample is
8
9 130 consecutively derived from heart transplant recipients undergoing their routine follow-up
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12 131 examination. Prior to their appointment, eligible patients are contacted via telephone and receive
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14 132 study information and questionnaires by mail, if interested.
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16

17 133 **Study Population**

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19 134 Inclusion criteria for the study are patients who are at least 18 years old, have undergone heart
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21 135 transplantation at least six months ago, and receive either Tacrolimus (Advagraf[®] or Prograf[®]),
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23 136 Cyclosporine (Sandimmun[®]) or Everolimus (Certican[®]) as their prescribed immunosuppressive
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25 137 medication. Patients with neurocognitive disabilities, who have no sufficient knowledge of the
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27 138 German language, and/or have severe mental disorders, will be excluded from the study. Medication
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29 139 adherence was no eligibility criterion. We specifically focus on medication implementation and
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31 140 exclude cases of initiation [1, 50]. Of app. 100 eligible patients per year, we expect a responder rate
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33 141 of app. 50%, resulting in a potential sample of 50 heart transplant recipients. We attain written
34
35 142 informed consent from all participating patients (see attachment files 1-2). The study was approved
36
37 143 by the Clinical Ethics Committee of the University Hospital Erlangen (Friedrich-Alexander-University,
38
39 144 Erlangen-Nürnberg, FAU).

40 145 **Study Design and Measurement Points**

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42 146 This is a prospective clinical observational trial. At study enrollment, each patient is asked to fill in a
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44 147 questionnaire battery on potential psychosocial predictors of NA and recommended lifestyle
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46 148 behaviors. Further, self-reports, collateral reports, and IS trough levels are assessed. Electronic
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48 149 monitoring will take place for three months. Meanwhile, each participant will receive phone calls in
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50 150 an interval of two weeks. Self-reports on potential incidents of NA referring to the last two weeks will
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3 151 be obtained. At the end of the study, patients will receive a feedback on their medication intake
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5 152 behavior. The timeline of our study procedure can be viewed in figure 1.
6
7 153 Figure 1
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10 154 **Measurement Methods**
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13 155 **Immunosuppressive Adherence Measures**
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16 156 ***Collateral Report***
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19 157 Adherence assessments are made after the patients' appointments with their treating physician. The
20
21 158 respective cardiologist is asked to rate the patients' IS adherence both on a 5-Point Likert Scale
22
23 159 (1=very good, 5=very bad) and on a 10cm (0-100%) Visual Analogue Scale (VAS) according to their
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25 160 subjective estimate of the patients' global adherence behavior. Similar measures were used in
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27 161 previous research [23, 24].
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30 162 ***Self-report***
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33 163 In order to assess self-reported NA, the patients equally receive a 10cm (0-100%) Visual Analogue
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35 164 Scale (VAS, part of the BAASIS© [20] Interview). We further apply the Basel Assessment of
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37 165 Adherence to Immunosuppressive Medication Scale (BAASIS© Questionnaire [20]), which consists of
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39 166 four items that relate to the medication taking behavior of the last 4 weeks. It assesses four types of
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41 167 IS non-adherence (dose taking, drug holiday, timing adherence >2h, and dose reduction) that can be
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43 168 rated on a 6-point scale (0=never/5=every day). Patients who consent to at least one of these four
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45 169 items are classified as non-adherent. We added a further question on timing adherence covering an
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47 170 additional intake interval of ±30min. During the course of the study, we also ask for the absolute
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49 171 frequency of IS intake deviations since the last phone call (recall period of app. 2 weeks).
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52 172 ***IS trough level variability***
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55 173 IS levels are routinely checked at each follow-up examination at the outpatient clinic, as well as at
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57 174 the patients' respective resident doctors every 8-10 weeks. We will use the IS trough level that is
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59 175 measured at study enrollment as well as up to three antecedent measures [51], since reliability
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3 176 improves with an increased number of measurements points [23, 52]. For frame of reference, each IS
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5 177 level is positioned with respect to its respective target level which can be changed individually by the
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7 178 treating cardiologist depending on the clinical course and time since transplantation. The graded
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9 179 standard target levels for the different immunosuppressive regimens can be viewed in the
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11 180 attachment file 3. We then will assess IS trough level variability (CV%[52]) that has been associated
12
13 181 with graft rejection, mortality, and NA [21, 22, 53]. For the calculation of CV%, each IS level will be
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15 182 standardized by dividing it by its respective target level. For each standardized IS trough level, we will
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17 183 calculate means and standard deviations. By dividing the standard deviation by the mean and
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19 184 multiplying it by 100, we will gain the CV% [52, 53]. Higher CV%s are associated with a higher
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21 185 fluctuation of IS trough levels [52]. The IS trough levels for the different IS regimens will be dealt with
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23 186 equally.

27
28 187 ***Electronic Monitoring***

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30 188 Electronic monitoring of NA is taking place with a multicompartiment pillbox (VAICA SimpleMed©)
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32 189 which provides medication storage for 7 days with up to 4 doses per day. Medication extraction is
33
34 190 automatically recorded and transferred to a web portal where the individual immunosuppressive
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36 191 medication schedules of each patient are registered. Data transfer is done using cellular reception.
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38 192 For timing adherence we set intervals at ±30minutes and ±2hours. Reminder functions
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40 193 (visual/acoustic signals) are disabled to keep a possible intervention effect at a minimum. In addition,
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42 194 participants are requested to keep a diary for incidence where IS extraction does not coincide with IS
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44 195 intake or the medication is taken from another source (pocket, take-away box, etc.). Irrespective of
45
46 196 each patient's dosing frequency and regimen, the percentage of (on time) taken
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48 197 immunosuppressants will be calculated per day, for each measurement point (T1-T6), as well as for
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50 198 the whole study course, attaining values between 0-100%. If the patient does not use the pill box for
51
52 199 a certain period (due to hospital stay, vacation, bad reception), the respective days are registered as
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54 200 missing.

1
2 201 **Psychosocial Variables**

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4 202 For the assessment of potential psychosocial predictors of NA, a variety of questionnaires are used.

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6 203 The applied measures are depicted in table 1.

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9
10 204 **Table 1 Psychosocial Constructs and applied questionnaires**

12 Psychosocial Construct	13 Instrument	14 Information
15 Depression	16 PHQ-9 [54, 55]	17 Self-report screening instrument of depression, 9 Items, 4-point scale
18 Perceived Social Support	19 FSozU-7 [56]	20 Self-report instrument on social support (practical support, emotional support, social integration), Short form of F-SozU, 7 items, 5-point scale
21 Perceived health related Quality of Life	22 WHOQoL-BREF [57]	23 Self-report instrument on perceived health related quality of life (physical health, psychological health, social relationships, environment), short from of WHOQoL-100, 26 items, 5-point scale
24 Self-Efficacy	25 SWE [58, 59]	26 Self-report questionnaire, 10 Items, 4-point scale
27 Attachment	28 RSQ [60, 61]	29 Self-report questionnaire , 30 Items, 5-point scale
30 Subjective experiences and attitudes towards immunosuppressive medication	31 MESI [62]	32 Self-report questionnaire, 7 Items, 5-point scale
33 Emotional Responses after Organ Transplantation	34 TxEQ [63, 64]	35 Self-report questionnaire on emotional responses after Tx (guilt, worry, disclosure, adherence, responsibility), 23 Items, 5-point scale
36 Satisfaction with Information about immunosuppressive medication	37 SIMS-D [65, 66]	38 Self-report questionnaire, 17 Items, 5-point scale
39 Perceptions of and Beliefs about medications	40 BMQ [67, 68]	41 Self-report questionnaire, 18 items, 5-point scale

42 205 **Non-pharmacological Non-Adherence and lifestyle behavior**

43 206 To assess non-pharmacological NA to recommended lifestyle behaviors we use self-report data on physical activity, diet, sun protection, smoking, appointment keeping, and alcohol use. For better comparability, we apply similar measurement methods used in previous research [29]. How each component is measured can be viewed in table 2.

44 210 **Table 2 Methods to assess non-pharmacological NA to recommended lifestyle behaviors**

51 Variable	52 Instrument	53 Information
54 Physical Activity	55 Brief Physical Activity Assessment tool [69]	56 2 items, frequency of intense and moderate physical activity during an average week (Adherent: sufficiently active, Non-adherent: insufficiently active)
57 Smoking	58 Self-developed (based on measure used by Helmy et al.[29])	59 1 Item on current smoking status, Adherent: Never Smoked/stopped before Htx, Non-Adherent: stopped after Htx,

			Smokes sometimes/several times a week/daily)
1	Alcohol use	Self-developed (based on measure used by Helmy et al.[29])	2 Items on current alcohol use (frequency of alcohol use per average week, usual quantity of alcohol intake), Non-Adherent: >1 drink/day (0.33l) (women), >2 drinks/d (men)
2	Sun protection	According to measure developed by Helmy et al.[29]	4 Items on current sun protection (using sun screen, wearing protective clothing, staying in the shade, being sensitive to the time of day), 5-point scale, Adherent: always using ≥1 of protection methods, Non-Adherent: not always using at least 1
3	Diet	According to measure developed by Helmy et al.[29]	1 items on adherence to general dietary recommendations, 4 items on daily diet (sugar, low calorie, low saturated fats, low salt), 5-point scale, Adherent: min. score 4-5 on all dietary recommendation, Non-Adherent: scores of 1-3 on any scale
4	Appointment Keeping	Self-developed (based on measure used by Helmy et al.[29])	1 Item, frequency of unexcused absence at scheduled follow-up appointments since transplantation (Adherent: 0, Non-Adherent: ≥1)

31 Note: HTx = Heart Transplantation.

32 211 Patient and Public Involvement

33 212 Patients and the public are not involved in the design, recruitment, and conduction of this study.

34 213 Statistical Analysis Plan

35 214 Data will be analyzed using SPSS 21 for Microsoft Windows© as well as the nlme-package [70] and
36 215 the lme4-package [71] for R version 3.5.1. For descriptive statistics we will depict frequencies, mean
37 216 values, standard deviations, and ranges. For group comparisons (Non-Responder-Analyses) we will
38 217 use independent T-tests, Mann-Whitney-U-tests, and Chi²-tests. Cohen's kappa and the Intraclass
39 218 Correlation Coefficient (ICC) will be used to conduct analyses on the association of measurement
40 219 methods and the relation between lifestyle behaviors and NA (RQ 1 and 3). For prospective analyses,
41 220 we will perform multiple linear regressions with the percentage frequency of electronically
42 221 monitored NA as the outcome variable (RQ 1 and 2). To assess changes in probability of adherence
43 222 over time, two alternative linear mixed models (strictly linear and piecewise linear) on the

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3 223 percentage frequency of NA of each measurement point (T1-T6) will be conducted (RQ 1). In order to
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5 224 examine potential risk factors for non-pharmacological adherence, logistic regression analyses will be
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7 225 applied (RQ 3). Results will be interpreted on a significance level of $p < .05$.
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10 226 **Progress**
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13 227 Recruitment started in September 2019. Of 48 eligible patients, 45 could be contacted via telephone
14
15 228 before their follow-up examination. Of those, 18 (40%) agreed to participate and are currently taking
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17 229 part in our study, whereas 27 declined participation. Reasons for refusal are lack of study interest,
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19 230 lack of time, sickness, and inconvenience or impossibility of integration of the pillbox into daily
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21 231 routine. Sociodemographic and biomedical data of all patients already included in our study are
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23 232 depicted in table 3.
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27 233 **Table 3 Sociodemographic and biomedical data of current participants**
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		Patients (N =18)
Age (M, SD, range)		56.93 (± 15.59), 32-82
Sex (n, %)	Males Females	18 (100) 0 (0)
Marital Status (n, %)	Single Married/in a relationship Separated/Divorced No information	3 (16.67) 11 (61.11) 1 (5.56) 3 (16.67)
Immunosuppressive Medication (n, %)	Advagraf \circledR (once daily) Prograf \circledR (twice daily) Sandimmun \circledR (twice daily) Certican \circledR (once daily) Combination of Certican \circledR and Sandimmun \circledR Comination of Certican \circledR and Prograf \circledR	1 (5.6) 7 (38.89) 6 (33.3) 2 (11.1) 1 (5.56) 1 (5.56)
Last transplantation (Median, SD, range)		2010 (± 4.72), 2003-2017

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47 234 **Discussion**
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50 235 To our knowledge, this is the first study assessing potential risk factors of immunosuppressive NA
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52 236 and non-pharmacological NA by prospectively applying electronic monitoring as the main NA
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54 237 measure. To date, no study has combined electronic monitoring, self-reports, physicians' estimates,
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56 238 and IS trough level variability to measure NA in HTRs. Although, measuring NA might induce an
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58 239 intervention effect resulting in temporarily improved adherence, adherence behavior is likely to
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3 240 stabilize on its base level after app. 35-40 days [72, 73]. Yet, by applying a combination of NA
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5 241 measures, especially electronic monitoring, more accurate statements about prevalences of NA and
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7 242 its potential risk factors in HTRs can be made. Precise measures and a detailed knowledge of
8
9 243 potential determinants are crucial in order to develop adequate adherence interventions and reduce
10
11 244 the fatal consequences of NA. In recent years, several well designed interventions for the
12
13 245 improvement of immunosuppressive adherence have been published [74-78]. Most of these
14
15 246 interventions are tailored to meet needs of renal transplant recipients. Interventions specifically for
16
17 247 HTRs are sparse or non-existent, especially since research on prevalences and risk factors of NA are
18
19 248 mostly focused on renal transplant recipients [4].
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23 249 Further, more research on lifestyle behaviors is required to fully understand its reasons as well as
24
25 250 potential implications on rejection and organ survival in HTRs. The potentially harmful consequences
26
27 251 of insufficient physical activity, inadequate sun protection, tobacco and alcohol use, and unhealthy
28
29 252 diet are already well-established in healthy populations [79-83]. But especially HTRs who are obliged
30
31 253 to life-long IS intake are at an even greater risk of developing chronic diseases and health issues
32
33 254 when engaging in unhealthy lifestyle behaviors [29, 84, 85]. In order to prevent comorbid diseases
34
35 255 and health damages, the development of interventions specifically targeting lifestyle habits and its
36
37 256 potential risk factors [33, 35] are substantial. Two recent studies on renal transplant recipients
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39 257 showed an improvement of sun-protective behavior after an educational intervention [86-88].
40
41 258 Interventions for the improvement of other lifestyle behaviors are lacking. For the development of
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43 259 adequate lifestyle interventions, the investigation of reasons and risk factors for these unhealthy
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45 260 behaviors is a prerequisite that we wish to meet with this study.
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49 261 If patients with acute forms of severe depression, excessive substance abuse or other self-harming
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51 262 behaviors are detected during study recruitment, immediate interventions or transfers to the
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53 263 respective outpatient clinics can be initiated.
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57 264 With the combination of lifestyle habits, psychosocial factors, and a bandwidth of
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59 265 immunosuppressive NA measures, especially electronic monitoring, our study will provide a
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3 266 promising opportunity to shed further light onto highly clinically relevant topics. We expect that our
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5 267 findings will contribute to the refinement of NA measures as well as the development of
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7 268 comprehensive interventions for HTRs.
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12 269 **Ethics and Dissemination** 13

14 270 The study was approved by the Clinical Ethics Committee of the University Hospital Erlangen
15
16 271 (Friedrich-Alexander-University, Erlangen-Nürnberg, FAU). Written informed consent is attained from
17
18 272 all participants. Patient data are pseudonymized. Each patient receives a three digit code under
19
20 273 which personal and medical data are saved. In a password protected file, the patients' name can be
21
22 274 linked to the three digit code to which only the study director has access to. At the end of the
23
24 275 project, the file on patient allocation will be deleted. The results of this study will be published in
25
26 276 peer-reviewed journals and presented at national and international conferences.
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32 277 Abbreviations:
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34 278 VAS: Visual Analogue Scale, NA: Non-Adherence, IS: Immunosuppressant/immunosuppressive, HTR: Renal Transplant
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36 279 Recipient, HTx: Heart Transplantation, ICC: Intraclass Correlation Coefficient
37
38

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40

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42
43 282 organization and conduction of this project. We especially would like to thank all patients who are taking part in our study.
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47 283 Competing Interests
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49 284 All authors declare that they have no competing interests
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53

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55
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57 287 Availability of data and material
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2
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4
5 289 Yesim Erim (yesim.erim@uk-erlangen.de)
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8
9 290 Author Contributions
10
11 291 ML designed and drafted the manuscript and is currently conducting the study. YE supervises and supports the
12 conceptualization and conduction of the study. MW enabled the initiation of this project and supervises study coordination.
13
14 293 MS supports patient recruitment. All authors (ML, MW, MS, YE) revised the manuscript critically for important intellectual
15 content, have given final approval of the version to be published and agree to be accountable for all aspects of the work in
16 ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and
17 resolved.
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322 pretransplant medication nonadherence as risk factor for post-transplant nonadherence to
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42 562 Figure titles and legends:

43 563 Figure 1. Timeline of study procedure. 2w = 2 weeks.

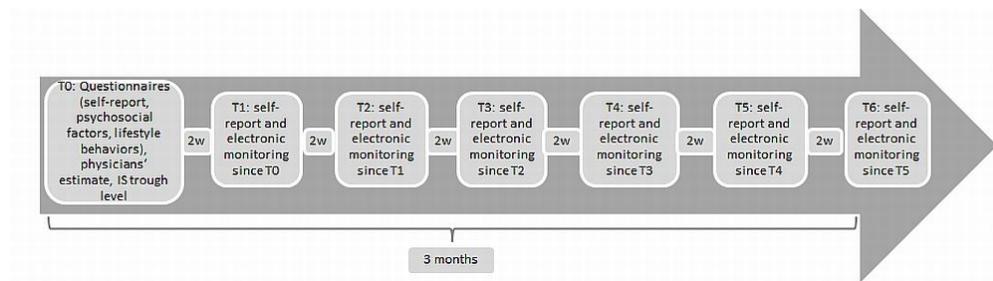


Figure 1. Timeline of study procedure. 2w = 2 weeks.

85x23mm (300 x 300 DPI)

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3 Attachment File 1: Declaration of consent as received by the patient
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9 Universitätsklinikum Erlangen 
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Datenschutzrechtliche Einwilligungserklärung

17 Hiermit erkläre ich,
18
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20 Frau/Herr geb. am,
21

22 dass ich an dem Forschungsprojekt „**Adhärenz und psychische Gesundheit nach Nieren-**
23 **und Herztransplantation“ (APT-Studie)** der psychosomatischen und
24 psychotherapeutischen Abteilung des Universitätsklinikums Erlangen und der
25 Herzchirurgischen Klinik teilnehmen möchte.

26 Ich habe die „Information zur Studienteilnahme“ gelesen und stimme den dort beschriebenen
27 Inhalten und Abläufen der Studie zu.

32 Ich bin damit einverstanden, dass die einleitend genannte Person bzw. ein Mitarbeiter der
33 einleitend genannten Institution Einblick in meine Original-Krankenunterlagen nimmt.

34 Ich stimme zu, dass Daten, die meine Person betreffen (hierzu gehören insbesondere auch
35 Krankheitsdaten aus meinen Krankenunterlagen) unter der Verantwortung der oben
36 genannten Institution in verschlüsselter Form für oben genannte Studie mit den jeweiligen
37 Fragestellungen gespeichert und verarbeitet werden.

Widerruf der Zustimmung zur Datenverwendung

44 Ich weiß, dass ich meine Zustimmung zur Verwendung meiner Daten jederzeit und ohne
45 Angabe von Gründen gegenüber der einleitend genannten Institution bzw. Person widerrufen
46 kann und dass dies keinen Einfluss auf meine etwaige weitere ärztliche Behandlung hat.

47 Im Falle des Widerrufs bin ich damit einverstanden, dass meine Daten zu Kontrollzwecken
48 weiterhin gespeichert bleiben. Ich habe jedoch das Recht, deren Löschung zu verlangen,
49 sofern gesetzliche Bestimmungen der Löschung nicht entgegenstehen. Bis zu einem
50 Widerruf bleibt die Datenverarbeitung rechtmäßig. Ich bin mir bewusst, dass im Falle einer
51 anonymisierten Speicherung meiner Daten deren Löschung auf meinen Wunsch nicht
52 möglich ist.

Hinweise zum Datenschutz**A. Allgemeine Angaben:**

- a. Name und Kontaktdaten der Verantwortlichen:

Durchführung der Studie:

Dipl.-Psych. Marietta Lieb

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Telefon: 09131-85-35928, Telefax: 09131-85-35952

E-Mail Adresse: yesim.erim@uk-erlangen.de

- b. Kontaktdaten des Datenschutzbeauftragten:

Herr Dr. Manfred Brunner

Telefon: 09131-85-46810, Telefax: 09131-85- 36783

E-Mail Adresse: manfred.brunner@uk-erlangen.de

- c. Rechtsgrundlage der Datenverarbeitung: Ihre Einwilligung

- d. Dauer der Speicherung: Entsprechend der gesetzlich vorgeschriebenen Archivierungsdauer für klinische Studien

- e. Beschwerderecht: Sie können sich an den Bayrischen Landesbeauftragten für Datenschutz (BayLfD), als Aufsichtsbehörde wenden, wenn Sie der Ansicht sind, dass die Verarbeitung Ihrer personenbezogenen Daten rechtswidrig erfolgt:

Bayrischer Landesbeauftragter für Datenschutzaufsicht (BayLfD)

Prof. Dr. Thomas Petri

Wagmüllerstraße 18, 80538 München

Telefon: 089 212672-0, E-Mail: poststelle@datenschutz-bayern.de

B. Allgemeine Rechte:

Das Recht auf Löschen und „Vergessenwerden“ ist eingeschränkt, soweit Ihre Daten für die wissenschaftliche Forschung erforderlich sind.

Näheres erfahren Sie hier:

1. Recht auf Löschung:

Sie haben das Recht, von dem Verantwortlichen zu verlangen, dass Sie betreffende personenbezogene Daten unverzüglich gelöscht werden, und der Verantwortliche ist verpflichtet, personenbezogene Daten unverzüglich zu löschen, sofern einer der folgenden Gründe zutrifft:

- 1
2
3 a) Die personenbezogenen Daten sind für die Zwecke, für die sie erhoben oder auf sonstige
4 Weise verarbeitet wurden, nicht mehr notwendig.
5 b) Sie widerrufen Ihre Einwilligung, auf die sich die Verarbeitung stützte, und es fehlt an einer
6 anderweitigen Rechtsgrundlage für Verarbeitung
7 c) Die personenbezogenen Daten wurden unrechtmäßig verarbeitet.
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9

10 **Sie haben keinen Anspruch auf Löschung, soweit Ihre Daten für wissenschaftliche Forschung
11 erforderlich sind und die Löschung voraussichtlich die Verwirklichung der Ziele dieser
12 Verarbeitung unmöglich macht oder ernsthaft beeinträchtigt,**

13 oder

14 die Verarbeitung zur Geltendmachung, Ausübung oder Verteidigung von Rechtsansprüchen erforderlich
15 ist.

16
17 2. Mitteilungspflicht im Zusammenhang mit der Berichtigung oder Löschung personenbezogener
18 Daten oder der Einschränkung der Verarbeitung:

19 Der Verantwortliche teilt allen Empfängern, denen personenbezogenen Daten offengelegt wurden,
20 jede Berichtigung oder Löschung der personenbezogenen Daten oder eine Einschränkung der
21 Verarbeitung mit, es sei denn, dies erweist sich als unmöglich oder ist mit einem
22 unverhältnismäßigen Aufwand verbunden. Der Verantwortliche unterrichtet Sie über diese
23 Empfänger, wenn Sie dies verlangen.

24
25 **Das Recht auf Datenübertragbarkeit ist eingeschränkt oder ausgeschlossen, wenn die Forschung
26 im öffentlichen Interesse liegt oder die Daten ein Geschäftsgeheimnis darstellen.**

27 Näheres erfahren Sie hier:

28
29 3. Recht auf Datenübertragbarkeit:

- 30 a) Sie haben das Recht, die Sie betreffenden personenbezogenen Daten, die Sie einem
31 Verantwortlichen bereitgestellt haben, in einem strukturierten, gängigen und
32 maschinenlesbaren Format zu erhalten, und Sie haben das Recht, diese Daten einem anderen
33 Verantwortlichen ohne Behinderung durch den Verantwortlichen, dem die personenbezogenen
34 Daten bereitgestellt wurden, zu übermitteln, sofern die Verarbeitung mithilfe automatisierter
35 Verfahren erfolgt.
36 b) Bei der Ausübung Ihres Rechts auf Datenübertragbarkeit gemäß Absatz a) haben Sie das
37 Recht, zu erwirken, dass die personenbezogenen Daten direkt von einem Verantwortlichen
38 einem anderen Verantwortlichen übermittelt werden, soweit dies technisch machbar ist.
39 c) Die Ausübung des Rechts auf Datenübertragbarkeit lässt das Recht auf Löschen der Daten
40 unberührt. Dieses Recht gilt nicht für eine Verarbeitung, die für die Wahrnehmung einer
41 Aufgabe erforderlich ist, die im öffentlichen Interesse liegt oder in Ausübung öffentlicher Gewalt
42 erfolgt, die dem Verantwortlichen übertragen wurde.
43 d) Das Recht gemäß Absatz 2 darf die Rechte und Freiheiten anderer Personen nicht
44 beeinträchtigen.

45
46 Hinweise:
47
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49 bei rein akademischer Forschung:

50 **Die in dieser Studie betriebene Forschung liegt im öffentlichen Interesse. Das Recht auf
51 Datenübertragbarkeit kann deshalb von Ihnen nicht ausgeübt werden.**

1
2
3
4 Werden personenbezogene Daten an ein Drittland oder an eine internationale Organisation übermittelt,
5 so haben Sie das Recht, über die geeigneten Garantien gemäß Artikel 46 DSGVO im Zusammenhang
6 mit der Übermittlung unterrichtet zu werden.
7
8

9 **C. Rechte, die durch den Forschungszweck beschränkt sind:**

10 Das Recht auf Berichtigung, Einschränkung der Verarbeitung und Auskunft ist ausgeschlossen, sofern
11 diese Rechte voraussichtlich die Verwirklichung des Forschungszweckes unmöglich machen oder
12 ernsthaft beeinträchtigen und die Beschränkung für die Erfüllung des Forschungszwecks notwendig ist.
13
14

15 Näheres erfahren Sie hier:
16

17 Sie haben als betroffene Person folgende Rechte, **sofern diese Rechte nicht voraussichtlich die**
18 **Verwirklichung des Forschungszwecks unmöglich machen oder ernsthaft beeinträchtigen und**
19 **die Beschränkung für die Erfüllung der Forschungszwecks notwendig ist:**
20
21

22 1. Recht auf Berichtigung:
23

24 Sie haben das Recht, von dem Verantwortlichen unverzüglich die Berichtigung Sie betreffender
25 unrichtiger personenbezogener Daten zu verlangen. Unter Berücksichtigung der Zwecke der
26 Verarbeitung haben Sie das Recht, die Vervollständigung unvollständiger personenbezogener Daten –
27 auch mittels einer ergänzenden Erklärung – zu verlangen.
28
29

30 2. Recht auf Einschränkung der Verarbeitung:
31

32 Sie haben das Recht, von dem Verantwortlichen die Einschränkung der Verarbeitung zu verlangen,
33 wenn eine der folgenden Voraussetzungen gegeben ist:
34

- 35 a) die Richtigkeit der personenbezogenen Daten wird von Ihnen bestritten. Die Einschränkung der
36 Verarbeitung kann in diesem Fall für eine Dauer verlangt werden, die es dem Verantwortlichen
37 ermöglicht, die Richtigkeit der personenbezogenen Daten zu überprüfen;
38 b) die Verarbeitung unrechtmäßig ist und Sie die Löschung der personenbezogenen Daten
39 ablehnen und stattdessen die Einschränkung der Nutzung der personenbezogenen Daten
40 verlangen;
41 c) der Verantwortliche die personenbezogenen Daten für die Zwecke der Verarbeitung nicht
42 länger benötigt, Sie sie jedoch zur Geltendmachung, Ausübung oder Verteidigung von
43 Rechtsansprüchen benötigen
44
45

46 Wurde die Verarbeitung eingeschränkt, so dürfen diese personenbezogenen Daten – von ihrer
47 Speicherung abgesehen – nur mit Ihrer Einwilligung oder zur Geltendmachung, Ausübung oder
48 Verteidigung von Rechtsansprüchen oder zum Schutz der Rechte einer anderen natürlichen oder
49 juristischen Person oder aus Gründen eines wichtigen öffentlichen Interesses der Union oder eines
50 Mitgliedstaats verarbeitet werden.
51
52

53 Haben Sie eine Einschränkung der Verarbeitung erwirkt, werden Sie von dem Verantwortlichen
54 unterrichtet, bevor die Einschränkung aufgehoben wird.
55
56

3. Auskunftsrechte:

Sie haben das Recht, von dem Verantwortlichen eine Bestätigung darüber zu verlangen, ob Sie betreffende personenbezogene Daten verarbeitet werden; ist dies der Fall, so haben Sie ein Recht auf Auskunft über diese personenbezogenen Daten und auf folgende Informationen:

- a) die Verarbeitungszwecke;
 - b) die Kategorien personenbezogener Daten, die verarbeitet werden;
 - c) die Empfänger oder Kategorien von Empfängern, gegenüber denen die personenbezogenen Daten offengelegt worden sind oder noch offengelegt werden, insbesondere bei Empfängern in Drittländern oder bei internationalen Organisationen;
 - d) falls möglich die geplante Dauer, für die die personenbezogenen Daten gespeichert werden, oder, falls dies nicht möglich ist, die Kriterien für die Festlegung dieser Dauer;
 - e) das Bestehen eines Beschwerderechts bei einer Aufsichtsbehörde;
 - f) Sie haben das Recht, vom Verantwortlichen eine Kopie der personenbezogenen Daten, die Gegenstand der Verarbeitung sind, zu erhalten. Für alle weiteren Kopien, die Sie beantragen, kann der Verantwortliche ein angemessenes Entgelt auf der Grundlage der Verwaltungskosten verlangen. Stellen Sie den Antrag elektronisch, so sind die Informationen in einem gängigen elektronischen Format zur Verfügung zu stellen, sofern Sie nichts Anderes angeben.

Das Recht auf Erhalt einer Kopie darf die Rechte und Freiheiten anderer Personen nicht beeinträchtigen.

Die Auskunftsrechte gem. 3. bestehen nicht, wenn die Daten für Zwecke der wissenschaftlichen Forschung erforderlich sind und die Auskunftserteilung einen unverhältnismäßigen Aufwand erfordern würde.

Datum Name der Probandin / des Probanden bzw.
der Patientin/ des Patienten Unterschrift

1 Attachment File 2: Study information as received by the patient
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Information zur Studienteilnahme

7
8
9
10 **Sehr geehrte Interessentin, sehr geehrter Interessent,**
11
12

13 die psychosomatische und psychotherapeutische Abteilung des Universitätsklinikums
14 Erlangen führt in Kooperation mit der Herzchirurgischen Klinik im Rahmen der
15 Transplantationsnachsorge eine Studie mit dem Titel „**Adhärenz und psychische**
16 **Gesundheit nach Nieren- und Herztransplantation**“ (**APT-Studie**) durch.
17
18

19 **Ziel der Studie ist es**, mithilfe einer elektronischen Pillenbox die regelmäßige Einnahme
20 (Adhärenz) der verschriebenen Immunsuppressiva zu überwachen, mit Ihrer
21 Selbsteinschätzung zu vergleichen, sowie mit psychologischen Faktoren in Verbindung zu
22 bringen. **Wie Sie wissen ist die regelmäßige Einnahme der Immunsuppressiva nach der**
23 **Transplantation ein für den Organerhalt immens wichtiger Beitrag von Ihnen.** Die
24 Studie zielt darauf ab, diese regelmäßige Einnahme zu untersuchen und zu verbessern.
25 Es ergeben sich keine Änderungen hinsichtlich Ihrer gewöhnlichen Nachsorgebehandlung
26 und die Studie ist mit keinerlei Risiken oder Kosten verbunden.
27
28

29
30 **Ablauf und Inhalte der Studie:**
31
32

33 Zunächst möchten wir Sie bitten die mitgesendeten Fragebögen zu beantworten und wenn
34 möglich bei Ihrem Termin zur Nachsorgeuntersuchung ausgefüllt mitzubringen.
35
36

37 **Während eines ersten persönlichen Termins (ca. 15-20 Minuten)**, direkt nach Ihrer
38 Untersuchung, erfolgt die **Ausgabe der elektronischen Pillenbox**. Dieses Gerät ist in
39 Deutschland zugelassen und wurde von uns in einer Vorstudie bezüglich der technischen
40 Eigenschaften überprüft. Zudem wurde das Gerät vom Datenbeauftragten des
41 Universitätsklinikums als unbedenklich eingeschätzt. Es erfolgt eine ausführliche Erklärung
42 und Demonstration der einfachen und benutzerfreundlichen Handhabung.
43
44

45 In einem **dreimonatigen Zeitraum** werden Sie **von zuhause aus** die Pillenbox anwenden,
46 während die Einnahme der Medikation automatisch aufgezeichnet wird. Es werden
47 **zweiwöchentlich Telefonate** (ca. 5 Minuten) stattfinden, während welcher sie vier Fragen
48 zu Ihrer Medikamenteneinnahme beantworten.
49
50

51 **Nach 3 Monaten** gibt es, wenn gewünscht, einen **weiteren persönlichen Termin**, während
52 dessen Sie ein **ausführliches Feedback** über Ihre Medikamenteneinnahme (Adhärenz)
53 erhalten, sowie die Pillenbox abgeben. Falls ein persönlicher Termin nicht möglich ist, kann
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1 die Box gerne auch auf dem Postweg zurückgegeben werden. Die Rückmeldung wäre in
2 diesem Fall auch telefonisch möglich.
3
4

5 **Informationen zum Datenschutz:**
6

7 Alle erhobenen Daten werden in **vollständig verschlüsselter Form** elektronisch
8 abgespeichert und nur zu Forschungszwecken verwendet. Jeder Teilnehmer erhält einen
9 **Probandencode**, welcher es erlaubt, die personenbezogenen Daten in pseudonymisierter
10 Form zusammenzuführen. Außenstehende können keinen Zusammenhang zwischen den
11 Daten und Ihrer Person herstellen. Nur die für die Studie verantwortlichen Personen haben
12 Zugang zu Ihren persönlichen Daten.
13
14

15 **Einwilligung zur Teilnahme und Widerrufsrecht:**
16

17 Ihre Teilnahme an der Untersuchung ist freiwillig und bedarf Ihrer datenschutzrechtlichen
18 Einwilligung (siehe Beiblatt „Datenschutzrechtliche Einwilligungserklärung“). Die einmalig
19 gegebene Zustimmung zur Studienteilnahme können Sie jederzeit ohne Angabe von
20 Gründen widerrufen, ohne dass Sie Nachteile für Ihre weitere medizinische Versorgung am
21 Universitätsklinikum Erlangen befürchten müssen.
22
23

24 Bei Fragen zur Studie steht Ihnen unsere Projektmitarbeiterin **Frau Dipl. Psych. Marietta**
25 **Lieb (Tel.: 09131-8545930; Email: marietta.lieb@uk-erlangen.de)** gerne zur Verfügung.
26
27

28
29
30 *Wir würden uns über Ihre Studienteilnahme sehr freuen und danken Ihnen im Voraus
31 recht herzlich für Ihre Unterstützung!*
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Attachment File 3: Graded target levels of the different immunosuppressive regimens

Immunosuppressive Medication	Time since transplantation	Target Level
Prograf/Advagraf®	< 6 months	12-15ng/ml
	7-12 months	10-15ng/ml
	> 12 months	7-10ng/ml
Sandimmun®	< 6months	250-350ng/ml
	6-12 months	200-250ng/ml
	>12 months	150-200ng/ml
Certican®	-----	3-8 µg/l
Prograf® + Certican®		
Prograf®	< 12 months	8-10ng/ml
	>12 months	6-7ng/ml
Certican®	-----	4-7 µg/l
Sandimmun® + Certican®		
Sandimmun®	-----	100-120ng/ml
Certican®	-----	3-8 µg/l

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A prospective single-center clinical observational study on electronically monitored medication non-adherence, its psychosocial risk factors and lifestyle behaviors after heart transplantation – A study protocol

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A Prospective Single-Center clinical observational Study on Electronically Monitored Medication Non-Adherence, its Psychosocial Risk Factors and Lifestyle Behaviors after Heart Transplantation – A Study Protocol

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Abstract

Introduction In heart transplant recipients (HTRs), non-adherence (NA) to immunosuppressive (IS) medication and to recommended lifestyle behaviors are a common phenomenon and associated with higher risk of allograft rejection, organ loss, and mortality. Risk factors for NA are highly diverse and still insufficiently researched. Precise measures of NA and an accurate understanding of its etiology are of undisputable importance to detect patients at risk and intervene accordingly. The aim of this study is to assess the accuracy and concordance of different measures for NA as well as to determine potential risk factors.

Methods and Analysis: This is a single-center prospective observational trial. HTRs who are at least aged 18, are no less than 6 months post-transplant and receive Tacrolimus (Prograf[®] or Advagraf[®]), Cyclosporine (Sandimmun[®]), or Everolimus (Certican[®]) as their prescribed IS medication are eligible for participation. We only include patients during the phase of medication implementation. At study enrollment, we assess depression, health related quality of life, self-efficacy, social support, attachment, experiences and attitudes towards immunosuppressive medication, emotional responses after transplantation, satisfaction with information about IS medication, and perceptions and beliefs

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2
3 26 about medications. We further ask patients to rate their lifestyle behaviors concerning alcohol,
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5 27 smoking, diet, physical activity, sun protection, and appointment keeping via questionnaires. Three
6
7 28 different measurement methods for NA are applied at T0: self-reports, physician's estimates, and IS
8
9 29 trough levels. NA is monitored prospectively using an electronic multicompartiment pillbox (MEMS,
10
11 30 VAICA©) over a 3-month period. Meanwhile, participants receive phone calls every second week to
12
13 31 obtain additional self-reports, resulting in a total of 7 measurement points.
14
15

16 32 **Ethics and Dissemination:** The study was approved by the Clinical Ethics Committee of the University
17
18 33 Hospital Erlangen (Friedrich-Alexander-University, Erlangen-Nürnberg). Written informed consent is
19
20 34 attained from all participants. The results of this study will be published in peer-reviewed journals and
21
22 35 presented at conferences.
23
24

25 36 **Keywords:** heart transplantation, electronic monitoring, self-reports, trough level variability, adherence,
26
27 37 psychosocial factors, lifestyle behavior, non-pharmacological adherence, prospective study, study protocol
28
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32 38 Article Summary
33

34 39 Strengths and Limitations of this study
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- 36
37 40 • This is the first study assessing potential risk factors of immunosuppressive NA and non-
38
39 41 pharmacological NA by prospectively applying electronic monitoring in heart transplant recipients
40
41 42 • This study combines different measurement methods for NA, such as electronic monitoring, self-
42
43 44 reports, physician's estimates, and IS trough level variability
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45 46 • One limitation of our study is a potential initial intervention effect induced by electronic
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47 48 monitoring; however, adherence behavior is likely to stabilize after app. 40 days
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49 46 • This is a single-center study with a moderate sample size
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52 47 **Trial registration number:** DRKS00020496
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54 48 Word count: 3281
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49 **Introduction**

50 Adherence is defined as “the process by which patients take their medication as prescribed” [1].

51 Especially in transplant recipients, regular and accurate intake of immunosuppressants is vital for organ

52 survival [2, 3]. Immunosuppressive non-adherence (NA) rates in transplant recipients differ greatly

53 depending on the respective organ, with a mean prevalence of app. 22.6% of patients per year [4-10].

54 For heart transplant recipients (HTRs), NA rates range between 4.6% and 39.2% [4-7, 11, 12],

55 influenced by the choice of measurement methods, operational definitions, and case finding methods.

56 Due to a rising awareness of its detrimental impact on allograft rejection, organ loss, and mortality [2,

57 13], research on NA in HTRs has increased substantially in recent years. Already minor deviations from

58 the medical regimen have been associated with hazardous effects on organ and patient survival [14].

59 Various assessment tools for NA are currently available, comprising both indirect and direct measures.

60 Direct measures include direct observation and blood assays, whereas for indirect measures pill

61 counts, self-reports, collateral reports, and electronic monitoring are used [15, 16]. The most

62 frequently employed NA measure for HTRs is self-report [16]. Despite their susceptibility to errors,

63 such as memory bias and social desirability, self-reports are considered practical and inexpensive tools

64 for NA assessment [15, 17-20]. Although electronic monitoring allows insights into patterns of

65 adherence behavior, its use can be quite expensive and labor-intensive [15, 17]. Except for few studies

66 [2, 5, 14], electronic monitoring is only very sparsely used in HTRs [16]. Blood assays such as the trough

67 level variability are also frequently applied as an adherence measure, since they have increasingly been

68 associated with rejection and mortality in HTRs [13, 21, 22]. Collateral reports, however, are mostly

69 considered unreliable measurement methods for NA [23]. To increase sensitivity, some studies also

70 use a combination of measurement methods to assess NA, which mostly results in very high NA rates

71 [5, 15]. Few studies have examined the accuracy and concordance of these NA measures [17, 24-28];

72 especially in HTRs, research is scarce. However, an accurate assessment of NA seems crucial in order

73 to detect patients at risk and to intervene accordingly.

1
2
3 74 Besides the relevancy of immunosuppressant intake, certain lifestyle habits can also adversely affect
4
5 75 organ survival as well as patient morbidity and mortality after transplantation [29-33]. Nonetheless, a
6
7 76 considerable amount of HTRs insufficiently adheres to certain lifestyle recommendations. Compared
8
9 77 to other types of organs, HTRs display particularly high NA rates for physical exercise, with prevalences
10
11 78 ranging between 33.7% and 49.1% [4, 11, 29, 34]. For following dietary recommendations, NA rates
12
13 79 between 22.9% and 46% were observed, while those for keeping follow-up appointments varied
14
15 80 between 5.7% and 37.3% [4, 11, 29, 30, 34]. Alcohol use was found for app. 4.9% to 27.8% of HTRs,
16
17 81 while tobacco use was confirmed by 3.2% to 9.1% [4, 11, 29, 34]. Helmy et al. [29] further revealed
18
19 82 that up to 39.9% of HTRs did not apply sun protection as recommended. Correlations between the
20
21 83 various domains of lifestyle habits could not be detected [11], whereas immunosuppressive NA was
22
23 84 found to be interrelated with appointment keeping [30] and smoking [12]. Research on non-
24
25 85 pharmacological NA is sparse and only few have examined the occurrence of and interrelations
26
27 86 between various NA areas. However, research on solid organ transplant recipients that included HTRs
28
29 87 found certain patient-related risk factors for unhealthy lifestyle behaviors. Post-transplant smoking
30
31 88 was found to be more prevalent in men, but less in older patients and those with comorbid physical
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33 89 diseases such as diabetes and hypertension [33]. Smoking in turn, was found to be a risk factor for
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35 90 post-transplant at-risk drinking, while post-transplant alcohol use in general could be linked with male
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37 91 gender, being employed, and a history of psychiatric illness, among others [35]. No significant risk
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39 92 factors were found for low physical exercise [36]. Most of these studies are based on results of kidney
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41 93 recipients, whilst research on heart recipients is rare. Especially studies connecting non-
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43 94 pharmacological NA with electronically monitored immunosuppressive NA in HTRs are missing.
44
45 95 Risk factors for immunosuppressive NA on the other hand are well examined, although highly diverse
46
47 96 and multifactorial in nature. They can reach from health system factors and behaviors of health care
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49 97 providers to factors on the individual patient level [37]. When developing interventions, especially the
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51 98 identification of modifiable factors on the patient level is of primary interest. A broad literature search
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53 99 on studies comprising HTRs revealed a variety of patient-related factors such as depression [38], lower
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3 100 social support [4, 6, 11, 39], lower quality of life [34], non-white ethnicity [4, 13], negative feelings [40,
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5 101 attitudes to medication or treatment [41-43], higher frequency of medication intake [44], longer
6
7 102 time since transplantation [6, 40, 42], and younger age [40] to be associated with NA. In renal
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9 103 transplant recipients, also anxiety [45], male sex [45, 46], lower self-efficacy [47-49], and avoidant
10
11 104 attachment [50] were found to be linked to increased NA. Although a considerable amount of research
12
13 105 is devoted to the reasons and risk factors for immunosuppressive NA, there is still a wide array of
14
15 106 contradictory and heterogeneous results. Further, research examining risk factors exclusively in HTRs
16
17 107 is sparse. Most studies examining risk factors for NA use self-reports, physicians' estimates, or through
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19 108 levels. To our knowledge, no study has examined potential risk factors for NA in HTRs that were
20
21 109 measured by applying electronic monitoring. What is more, studies on risk factors for NA to
22
23 110 recommended lifestyle behaviors are missing. In order to develop adequate adherence interventions,
24
25 111 assessing the accuracy of NA measures as well as determining factors that promote NA is of paramount
26
27 112 importance. With this study, we cover relevant topics on adherence after heart transplantation and
28
29 113 wish to fill substantial gaps in current research.
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37 114 **Study Aims**
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39 115 The aim of our study is to investigate electronically monitored NA in heart transplant recipients over a
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41 116 period of 3 months during the phase of medication implementation [1, 51]. The following three
42
43 117 research questions (RQ) will be addressed:
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45
46 118 1) Measurement Methods: Do different measurement methods of NA correlate with each other
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48 119 at the beginning of the study? Does electronically monitored NA coincide with self-reported
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50 120 NA during the course of the study?
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53 121 2) Psychosocial Predictors: Can certain psychosocial factors predict electronically monitored NA
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55 122 in HTRs?
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3 123 3) Non-pharmacological adherence and Lifestyle Behaviors: To what extend do heart transplant
4 recipients comply with lifestyle requirements? Does immunosuppressive medication coincide
5
6 124 with healthy lifestyle behaviors? What are potential risk factors for these behaviors?
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126 **Methods and Analysis**

13

14 **Setting and Recruitment**

15
16 127 This work is part of the APT (Adherence and Psychological Health after Transplantation) research
17 project of the Department of Psychosomatic Medicine and Psychotherapy and takes place in
18 cooperation with the Department of Cardiac Surgery and the Department of Nephrology and
19 Hypertension in Erlangen. This sub-study is conducted at the outpatient clinic of the Department of
20 Cardiac Surgery of the University Hospital of Erlangen. During the course of one year, the sample is
21 consecutively derived from heart transplant recipients undergoing their routine follow-up
22 examination. Prior to their appointment, eligible patients are contacted via telephone and receive
23 study information and questionnaires by mail, if interested.
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37 **Study Population**

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39 136 Inclusion criteria for the study are patients who are at least 18 years old, have undergone heart
40 transplantation at least 6 months ago, and receive either Tacrolimus (Advagraf \circledR or Prograf \circledR),
41 Cyclosporine (Sandimmun \circledR) or Everolimus (Certican \circledR) as their prescribed immunosuppressive
42 medication. Patients with neurocognitive disabilities, who have no sufficient knowledge of the German
43 language, and/or have severe mental disorders will be excluded from the study. Medication adherence
44 was no eligibility criterion. We specifically focus on medication implementation and exclude cases of
45 initiation [1, 51]. Of app. 100 eligible patients per year, we expect a responder rate of app. 50%,
46 resulting in a potential sample of 50 heart transplant recipients. We attain written informed consent
47 from all participating patients (see attachment files 1-2). The study was approved by the Clinical Ethics
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3 146 Committee of the University Hospital Erlangen (Friedrich-Alexander-University, Erlangen-Nürnberg,
4
5 147 FAU).
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9 148 **Study Design and Measurement Points**

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11 149 This is a prospective clinical observational trial. At study enrollment, each patient is asked to fill in a
12
13 150 questionnaire battery on potential psychosocial predictors of NA and recommended lifestyle
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15 151 behaviors. Further, self-reports, collateral reports, and IS trough levels are assessed. Electronic
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17 152 monitoring will take place for 3 months. Meanwhile, each participant will receive phone calls in an
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19 153 interval of two weeks. Self-reports on potential incidents of NA referring to the last two weeks will be
20
21 154 obtained. At the end of the study, patients will receive a feedback on their medication intake behavior.
22
23
24 155 The timeline of our study procedure can be viewed in figure 1.
25
26 156 Figure 1

27
28
29 157 **Measurement Methods**
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31
32 158 **Immunosuppressive Adherence Measures**
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34
35 159 ***Collateral Report***
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37 160 Adherence assessments are made after the patients' appointments with their treating physician. The
38
39 161 respective cardiologist is asked to rate the patients' immunosuppressive adherence both on a 5-Point
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41 162 Likert Scale (1=very good, 5=very bad) and on a 10cm (0-100%) Visual Analogue Scale (VAS) according
42
43 163 to their subjective estimate of the patients' global adherence behavior. Similar measures were used in
44
45 164 previous research [23, 24].
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49
50 165 ***Self-report***
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52 166 As a means to assess self-reported NA, the patients equally receive a 10cm (0-100%) Visual Analogue
53
54 167 Scale (VAS, part of the BAASIS© [20] Interview), in order to reach comparability with the collateral
55
56 168 report. We further apply the Basel Assessment of Adherence to Immunosuppressive Medication Scale
57
58 169 (BAASIS© Questionnaire [20]), which consists of four items that relate to the medication taking
59
60 170 behavior of the last 4 weeks. It assesses four types of immunosuppressive NA (dose taking, drug

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2
3 171 holiday, timing adherence >2h, and dose reduction) that can be rated on a 6-point scale
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5 172 (0=never/5=every day). Patients who consent to at least one of these four items are classified as non-
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7 173 adherent. We added a further question on timing adherence covering an additional intake interval of
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9 174 ±30min. During the course of the study, we also ask for the absolute frequency of immunosuppressive
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11 175 intake deviations since the last phone call (recall period of app. 2 weeks).
12
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15 176 ***IS trough level variability***
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17 177 Immunosuppression levels (IS levels) are routinely checked at each follow-up examination at the
18
19 178 outpatient clinic, as well as at the patients' respective resident doctors every 8-10 weeks. We will use
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21 179 the IS trough level that is measured at study enrollment as well as up to three antecedent measures
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23 180 [52], since reliability improves with an increased number of measurements points [23, 53]. For frame
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25 181 of reference, each IS level is positioned with respect to its respective target level which can be changed
26
27 182 individually by the treating cardiologist depending on the clinical course and time since
28
29 183 transplantation. The graded standard target levels for the different immunosuppressive regimens can
30
31 184 be viewed in the attachment file 3. We then will assess IS trough level variability (CV%[53]) that has
32
33 185 been associated with graft rejection, mortality, and NA [21, 22, 54]. For the calculation of CV%, each
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35 186 IS level will be standardized by dividing it by its respective target level. For each standardized IS trough
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37 187 level, we will calculate means and standard deviations. By dividing the standard deviation by the mean
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39 188 and multiplying it by 100, we will gain the CV% [53, 54]. Higher CV%s are associated with a higher
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41 189 fluctuation of IS trough levels [53]. The IS trough levels for the different IS regimens will be dealt with
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43 190 equally.
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49 191 ***Electronic Monitoring***
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51 192 Electronic monitoring of NA is taking place with a multicompartiment pillbox (VAICA SimpleMed©)
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53 193 which provides medication storage for 7 days with up to 4 doses per day. Medication extraction is
54
55 194 automatically recorded and transferred to a web portal where the individual immunosuppressive
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57 195 medication schedules of each patient are registered. Data transfer is done using cellular reception. For
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59 196 timing adherence we set intervals at ±30minutes and ±2hours. Reminder functions (visual/acoustic
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3 signals) are disabled to keep a possible intervention effect at a minimum. In addition, participants are
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5 requested to keep a diary for incidences when medication extraction does not coincide with pill intake
6
7 or the medication is taken from another source (pocket, take-away box, etc.). Irrespective of each
8
9 patient's dosing frequency and regimen, the percentage of (on time) taken immunosuppressants will
10
11 be calculated per day, for each measurement point (T1-T6), as well as for the whole study course,
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13 attaining values between 0%-100%. If the patient does not use the pill box for a certain period (due to
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15 hospital stay, vacation, bad reception), the respective days are registered as missing.
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19 **204 Psychosocial Variables**
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22 For the assessment of patient-related psychosocial risk factors, a variety of instruments is applied (see
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24 table 1). The choice of potential determinants is limited to individual patient-related factors amenable
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26 to change and modifiable by interventions.
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29 **208 Table 1 Psychosocial Constructs and applied questionnaires**
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31 Psychosocial Construct	32 Instrument	33 Information
34 Depression	35 PHQ-9 [55, 56]	36 Self-report screening instrument of depression, 9 Items, 4-point 37 scale
38 Perceived Social Support	39 FSozU-7 [57]	40 Self-report instrument on social support (practical support, 41 emotional support, social integration), Short form of F-SozU, 42 7 items, 5-point scale
43 Perceived health related Quality of Life	44 WHOQoL-BREF 45 [58]	46 Self-report instrument on perceived health related quality of life 47 (physical health, psychological health, social relationships, 48 environment), short from of WHOQoL-100, 26 items, 5-point 49 scale
50 Self-Efficacy	51 SWE [59, 60]	52 Self-report questionnaire, 10 Items, 4-point scale
53 Attachment	54 RSQ [61, 62]	55 Self-report questionnaire , 30 Items, 5-point scale
56 Subjective experiences and attitudes towards 57 immunosuppressive medication	58 MESI [63]	59 Self-report questionnaire, 7 Items, 5-point scale
60 Emotional Responses after Organ Transplantation	61 TxEQ [64, 65]	62 Self-report questionnaire on emotional responses after Tx (guilt, 63 worry, disclosure, adherence, responsibility), 23 Items, 5-point 64 scale
65 Satisfaction with Information about immunosuppressive medication	66 SIMS-D [66, 67]	67 Self-report questionnaire, 17 Items, 5-point scale
68 Perceptions of and Beliefs about medications	69 BMQ [68, 69]	70 Self-report questionnaire, 18 items, 5-point scale

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72 **209 Non-pharmacological Non-Adherence and lifestyle behavior**
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74 To assess non-pharmacological NA to recommended lifestyle behaviors we use self-report data on
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76 physical activity, diet, sun protection, smoking, appointment keeping, and alcohol use. For better
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3 212 comparability, we apply similar measurement methods used in previous research [29]. How each
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5 213 component is measured can be viewed in table 2.
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8 214 **Table 2 Methods to assess non-pharmacological NA to recommended lifestyle behaviors**

10	11	Variable	Instrument	Information
12	13	Physical Activity	Brief Physical Activity Assessment tool [70]	2 items, frequency of intense and moderate physical activity during an average week (Adherent: sufficiently active, Non-adherent: insufficiently active)
14	15	Smoking	Self-developed (based on measure used by Helmy et al.[29])	1 Item on current smoking status, Adherent: Never Smoked/stopped before Htx, Non-Adherent: stopped after Htx, Smokes sometimes/several times a week/daily)
16	17	Alcohol use	Self-developed (based on measure used by Helmy et al.[29])	2 Items on current alcohol use (frequency of alcohol use per average week, usual quantity of alcohol intake), Non-Adherent: >1 drink/day (0.33l) (women), >2 drinks/d (men)
18	19	Sun protection	According to measure developed by Helmy et al.[29]	4 Items on current sun protection (using sun screen, wearing protective clothing, staying in the shade, being sensitive to the time of day), 5-point scale, Adherent: always using ≥1 of protection methods, Non-Adherent: not always using at least 1
20	21	Diet	According to measure developed by Helmy et al.[29]	1 items on adherence to general dietary recommendations, 4 items on daily diet (sugar, low calorie, low saturated fats, low salt), 5-point scale, Adherent: min. score 4-5 on all dietary recommendation, Non-Adherent: scores of 1-3 on any scale
22	23	Appointment Keeping	Self-developed (based on measure used by Helmy et al.[29])	1 Item, frequency of unexcused absence at scheduled follow-up appointments since transplantation (Adherent: 0, Non-Adherent: ≥1)

48 Note: HTx = Heart Transplantation.

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50 215 **Patient and Public Involvement**

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52 216 Patients and the public are not involved in the design, recruitment, and conduction of this study.

53
54 217 **Statistical Analysis Plan**

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56 218 Data will be analyzed using SPSS 21 for Microsoft Windows© as well as the nlme-package [71] and the
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58 219 lme4-package [72] for R version 3.5.1. For descriptive statistics we will depict frequencies, mean

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3 220 values, standard deviations, and ranges. For group comparisons (Non-Responder-Analyses) we will use
4 independent T-tests, Mann-Whitney-U-tests, and Chi²-tests. Cohen's kappa and the Intraclass
5 Correlation Coefficient (ICC) will be used to conduct analyses on the association of measurement
6 methods and the relation between lifestyle behaviors and NA (RQ 1 and 3). For prospective analyses,
7 we will perform multiple linear regressions with the percentage frequency of electronically monitored
8 NA as the outcome variable (RQ 1 and 2). To assess changes in probability of adherence over time, two
9 alternative linear mixed models (strictly linear and piecewise linear) on the percentage frequency of
10 NA of each measurement point (T1-T6) will be conducted (RQ 1). In order to examine potential risk
11 factors for non-pharmacological adherence, logistic regression analyses will be applied (RQ 3). If
12 predictor count in regression analyses is restricted due to limited sample size, we will conduct
13 preliminary analyses (eg. Spearman's ρ , Pearson's r , ICC) in order to insert only variables that
14 significantly correlate with the outcome. Bonferroni-Holm corrections will be made for all statistical
15 tests in order to adjust for the alpha-error of multiple testing. Results will be interpreted on a
16 significance level of $p < .05$.
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35 234 **Progress**
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38 235 Recruitment started in September 2019. Of 48 eligible patients, 45 could be contacted via telephone
39 before their follow-up examination. Of those, 18 (40%) agreed to participate and are currently taking
40 part in our study, whereas 27 declined participation. Reasons for refusal are lack of study interest, lack
41 of time, sickness, and inconvenience or impossibility to integrate the pillbox into daily routine.
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49 239 Sociodemographic and biomedical data of all patients already included in our study are depicted in
50 table 3.
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53 241 **Table 3 Sociodemographic and biomedical data of current participants**

	Patients (N =18)	
Age (M, SD, range)	56.93 (± 15.59), 32-82	
Sex (n, %)	Males	18 (100)
	Females	0 (0)
Marital Status (n, %)	Single	3 (16.67)
	Married/in a relationship	11 (61.11)

	Separated/Divorced	1 (5.56)
	No information	3 (16.67)
5	Immunosuppressive Medication (n, %)	
6	Advagraf© (once daily)	1 (5.6)
7	Prograf© (twice daily)	7 (38.89)
8	Sandimmun© (twice daily)	6 (33.3)
9	Certican© (twice daily)	2 (11.1)
10	Combination of Certican© and Sandimmun©	1 (5.56)
11	Combination of Certican© and Prograf©	1 (5.56)
12	Last transplantation (Median, SD, range)	2010 (± 4.72), 2003-2017

242 Discussion

243 To our knowledge, this is the first study assessing potential risk factors of immunosuppressive NA and
244 non-pharmacological NA by prospectively applying electronic monitoring as the main NA measure. To
245 date, no study has combined electronic monitoring, self-reports, physicians' estimates, and IS trough
246 level variability to measure NA in HTRs. Although, measuring NA might induce an intervention effect
247 resulting in temporarily improved adherence, adherence behavior is likely to stabilize on its base level
248 after app. 35-40 days [73, 74]. Yet, by applying a combination of NA measures, especially electronic
249 monitoring, more accurate statements about prevalences of NA and its potential risk factors in HTRs
250 can be made. Precise measures and a detailed knowledge of potential determinants are crucial in order
251 to develop adequate adherence interventions and reduce the fatal consequences of NA. In recent
252 years, several well designed interventions for the improvement of immunosuppressive adherence
253 have been published [75-79]. Most of these interventions are tailored to meet needs of renal
254 transplant recipients. Interventions specifically for HTRs are sparse or non-existent, especially since
255 research on prevalences and risk factors of NA are mostly focused on renal transplant recipients [4].
256 Further, more research on lifestyle behaviors is required to fully understand its reasons as well as
257 potential implications on rejection and organ survival in HTRs. The potentially harmful consequences
258 of insufficient physical activity, inadequate sun protection, tobacco and alcohol use, and unhealthy
259 diet are already well-established in healthy populations [80-84]. But especially HTRs who are obliged
260 to life-long immunosuppression intake are at an even greater risk of developing chronic diseases and
261 health issues when engaging in unhealthy lifestyle behaviors [29, 85, 86]. In order to prevent comorbid
262 diseases and health damages, the development of interventions specifically targeting lifestyle habits

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3 263 and its potential risk factors [33, 35] are substantial. Two recent studies on renal transplant recipients
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5 264 showed an improvement of sun-protective behavior after an educational intervention [87-89].
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7 265 Interventions for the improvement of other lifestyle behaviors are lacking. For the development of
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9 266 adequate lifestyle interventions, the investigation of reasons and risk factors for these unhealthy
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11 267 behaviors is a prerequisite that we wish to meet with this study.
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14 268 If patients with acute forms of severe depression, excessive substance abuse or other self-harming
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16 269 behaviors are detected during study recruitment, immediate interventions or transfers to the
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18 270 respective outpatient clinics can be initiated.
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21 271 With the combination of lifestyle habits, psychosocial factors, and a bandwidth of immunosuppressive
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23 272 NA measures, especially electronic monitoring, our study will provide a promising opportunity to shed
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25 273 further light onto highly clinically relevant topics. We expect that our findings will contribute to the
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27 274 refinement of NA measures as well as the development of comprehensive interventions for HTRs.
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32 275 **Ethics and Dissemination**
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34
35 276 The study was approved by the Clinical Ethics Committee of the University Hospital Erlangen (Friedrich-
36
37 277 Alexander-University, Erlangen-Nürnberg, FAU). Written informed consent is attained from all
38
39 278 participants. Patient data are pseudonymized. Each patient receives a three digit code under which
40
41 279 personal and medical data are saved. In a password protected file, the patients' name can be linked to
42
43 280 the three digit code to which only the study director has access to. At the end of the project, the file
44
45 281 on patient allocation will be deleted. The results of this study will be published in peer-reviewed
46
47 282 journals and presented at national and international conferences.
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50 283 Abbreviations:
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52 284 VAS: Visual Analogue Scale, NA: Non-Adherence, HBM: Health Belief Model, IS: Immunosuppressant/immunosuppressive,
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54 285 HTR: Renal Transplant Recipient, HTx: Heart Transplantation, ICC: Intraclass Correlation Coefficient
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10 290 All authors declare that they have no competing interests
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15
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18
19 293 Availability of data and material
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22
23 295 Yesim Erim (yesim.erim@uk-erlangen.de)
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26
27 296 Author Contributions
28
29 297 ML designed and drafted the manuscript and is currently conducting the study. YE supervises and supports the
30 conceptualization and conduction of the study. MW enabled the initiation of this project and supervises study coordination.
31
32 299 MS supports patient recruitment. All authors (ML, MW, MS, YE) revised the manuscript critically for important intellectual
33
34 300 content, have given final approval of the version to be published and agree to be accountable for all aspects of the work in
35
36 301 ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and
37
38 302 resolved.
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41 551 Figure titles and legends:

42 552 Figure 1. Timeline of study procedure. 2w = 2 weeks.
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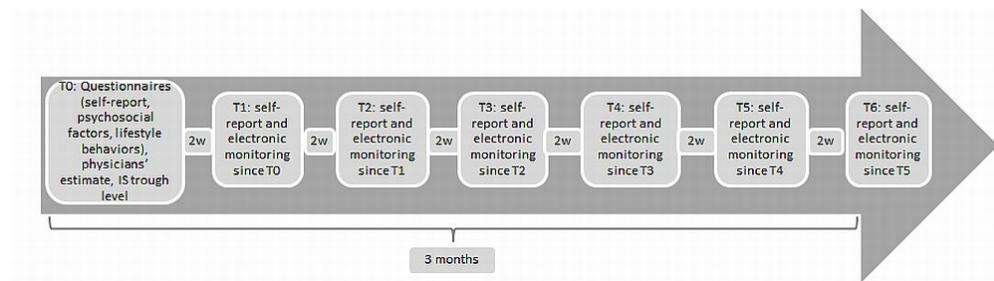


Figure 1. Timeline of study procedure. 2w = 2 weeks.

85x23mm (300 x 300 DPI)

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3 Attachment File 1: Declaration of consent as received by the patient (German and English)
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7
8
9 Universitätsklinikum
Erlangen 
10
11
12 **Datenschutzrechtliche Einwilligungserklärung**
13
14
15
16
17 Hiermit erkläre ich,
18
19 **Frau/Herr** , geb. am.,
20
21
22 dass ich an dem Forschungsprojekt „**Adhärenz und psychische Gesundheit nach Nieren-**
23 **und Herztransplantation“ (APT-Studie)** der psychosomatischen und
24 psychotherapeutischen Abteilung des Universitätsklinikums Erlangen und der
25 Herzchirurgischen Klinik teilnehmen möchte.
26
27 Ich habe die „Information zur Studienteilnahme“ gelesen und stimme den dort beschriebenen
28
29 Inhalten und Abläufen der Studie zu.
30
31
32 Ich bin damit einverstanden, dass die einleitend genannte Person bzw. ein Mitarbeiter der
33 einleitend genannten Institution Einblick in meine Original-Krankenunterlagen nimmt.
34
35 Ich stimme zu, dass Daten, die meine Person betreffen (hierzu gehören insbesondere auch
36 Krankheitsdaten aus meinen Krankenunterlagen) unter der Verantwortung der oben
37 genannten Institution in verschlüsselter Form für oben genannte Studie mit den jeweiligen
38 Fragestellungen gespeichert und verarbeitet werden.
39
40
41
42
43
44
45 **Widerruf der Zustimmung zur Datenverwendung**
46 Ich weiß, dass ich meine Zustimmung zur Verwendung meiner Daten jederzeit und ohne
47 Angabe von Gründen gegenüber der einleitend genannten Institution bzw. Person widerrufen
48 kann und dass dies keinen Einfluss auf meine etwaige weitere ärztliche Behandlung hat.
49
50 Im Falle des Widerrufs bin ich damit einverstanden, dass meine Daten zu Kontrollzwecken
51 weiterhin gespeichert bleiben. Ich habe jedoch das Recht, deren Löschung zu verlangen,
52 sofern gesetzliche Bestimmungen der Löschung nicht entgegenstehen. Bis zu einem
53 Widerruf bleibt die Datenverarbeitung rechtmäßig. Ich bin mir bewusst, dass im Falle einer
54 anonymisierten Speicherung meiner Daten deren Löschung auf meinen Wunsch nicht
55 möglich ist.
56
57
58
59
60

Hinweise zum Datenschutz**A. Allgemeine Angaben:**

- a. Name und Kontaktdaten der Verantwortlichen:

Durchführung der Studie:

Dipl.-Psych. Marietta Lieb

Psychosomatische und Psychotherapeutische Abteilung

Schwabachanlage 6, 91054 Erlangen

Telefon: 09131-85-45930

E-Mail Adresse: marietta.lieb@uk-erlangen.de

Studienleitung:

Prof. Dr. (TR) Yesim Erim

Psychosomatische und Psychotherapeutische Abteilung

Schwabachanlage 6, 91054 Erlangen

Telefon: 09131-85-35928, Telefax: 09131-85-35952

E-Mail Adresse: yesim.erim@uk-erlangen.de

- b. Kontaktdaten des Datenschutzbeauftragten:

Herr Dr. Manfred Brunner

Telefon: 09131-85-46810, Telefax: 09131-85- 36783

E-Mail Adresse: manfred.brunner@uk-erlangen.de

- c. Rechtsgrundlage der Datenverarbeitung: Ihre Einwilligung

- d. Dauer der Speicherung: Entsprechend der gesetzlich vorgeschriebenen Archivierungsdauer für klinische Studien

- e. Beschwerderecht: Sie können sich an den Bayrischen Landesbeauftragten für Datenschutz (BayLfD), als Aufsichtsbehörde wenden, wenn Sie der Ansicht sind, dass die Verarbeitung Ihrer personenbezogenen Daten rechtswidrig erfolgt:

Bayrischer Landesbeauftragter für Datenschutzaufsicht (BayLfD)

Prof. Dr. Thomas Petri

Wagmüllerstraße 18, 80538 München

Telefon: 089 212672-0, E-Mail: poststelle@datenschutz-bayern.de

B. Allgemeine Rechte:

Das Recht auf Löschen und „Vergessenwerden“ ist eingeschränkt, soweit Ihre Daten für die wissenschaftliche Forschung erforderlich sind.

Näheres erfahren Sie hier:

1. Recht auf Löschung:

Sie haben das Recht, von dem Verantwortlichen zu verlangen, dass Sie betreffende personenbezogene Daten unverzüglich gelöscht werden, und der Verantwortliche ist verpflichtet, personenbezogene Daten unverzüglich zu löschen, sofern einer der folgenden Gründe zutrifft:

- 1
2
3 a) Die personenbezogenen Daten sind für die Zwecke, für die sie erhoben oder auf sonstige
4 Weise verarbeitet wurden, nicht mehr notwendig.
5 b) Sie widerrufen Ihre Einwilligung, auf die sich die Verarbeitung stützte, und es fehlt an einer
6 anderweitigen Rechtsgrundlage für Verarbeitung
7 c) Die personenbezogenen Daten wurden unrechtmäßig verarbeitet.
8
9

10 **Sie haben keinen Anspruch auf Löschung, soweit Ihre Daten für wissenschaftliche Forschung
11 erforderlich sind und die Löschung voraussichtlich die Verwirklichung der Ziele dieser
12 Verarbeitung unmöglich macht oder ernsthaft beeinträchtigt,**

13 oder

14 die Verarbeitung zur Geltendmachung, Ausübung oder Verteidigung von Rechtsansprüchen erforderlich
15 ist.

16
17 2. Mitteilungspflicht im Zusammenhang mit der Berichtigung oder Löschung personenbezogener
18 Daten oder der Einschränkung der Verarbeitung:

19 Der Verantwortliche teilt allen Empfängern, denen personenbezogenen Daten offengelegt wurden,
20 jede Berichtigung oder Löschung der personenbezogenen Daten oder eine Einschränkung der
21 Verarbeitung mit, es sei denn, dies erweist sich als unmöglich oder ist mit einem
22 unverhältnismäßigen Aufwand verbunden. Der Verantwortliche unterrichtet Sie über diese
23 Empfänger, wenn Sie dies verlangen.

24
25 **Das Recht auf Datenübertragbarkeit ist eingeschränkt oder ausgeschlossen, wenn die Forschung
26 im öffentlichen Interesse liegt oder die Daten ein Geschäftsgeheimnis darstellen.**

27 Näheres erfahren Sie hier:

28
29 3. Recht auf Datenübertragbarkeit:

- 30 a) Sie haben das Recht, die Sie betreffenden personenbezogenen Daten, die Sie einem
31 Verantwortlichen bereitgestellt haben, in einem strukturierten, gängigen und
32 maschinenlesbaren Format zu erhalten, und Sie haben das Recht, diese Daten einem anderen
33 Verantwortlichen ohne Behinderung durch den Verantwortlichen, dem die personenbezogenen
34 Daten bereitgestellt wurden, zu übermitteln, sofern die Verarbeitung mithilfe automatisierter
35 Verfahren erfolgt.
36 b) Bei der Ausübung Ihres Rechts auf Datenübertragbarkeit gemäß Absatz a) haben Sie das
37 Recht, zu erwirken, dass die personenbezogenen Daten direkt von einem Verantwortlichen
38 einem anderen Verantwortlichen übermittelt werden, soweit dies technisch machbar ist.
39 c) Die Ausübung des Rechts auf Datenübertragbarkeit lässt das Recht auf Löschen der Daten
40 unberührt. Dieses Recht gilt nicht für eine Verarbeitung, die für die Wahrnehmung einer
41 Aufgabe erforderlich ist, die im öffentlichen Interesse liegt oder in Ausübung öffentlicher Gewalt
42 erfolgt, die dem Verantwortlichen übertragen wurde.
43 d) Das Recht gemäß Absatz 2 darf die Rechte und Freiheiten anderer Personen nicht
44 beeinträchtigen.

45
46 Hinweise:
47
48

49 bei rein akademischer Forschung:

50 **Die in dieser Studie betriebene Forschung liegt im öffentlichen Interesse. Das Recht auf
51 Datenübertragbarkeit kann deshalb von Ihnen nicht ausgeübt werden.**

1
2
3
4 Werden personenbezogene Daten an ein Drittland oder an eine internationale Organisation übermittelt,
5 so haben Sie das Recht, über die geeigneten Garantien gemäß Artikel 46 DSGVO im Zusammenhang
6 mit der Übermittlung unterrichtet zu werden.
7
8

9 **C. Rechte, die durch den Forschungszweck beschränkt sind:**

10 Das Recht auf Berichtigung, Einschränkung der Verarbeitung und Auskunft ist ausgeschlossen, sofern
11 diese Rechte voraussichtlich die Verwirklichung des Forschungszweckes unmöglich machen oder
12 ernsthaft beeinträchtigen und die Beschränkung für die Erfüllung des Forschungszwecks notwendig ist.
13
14

15 Näheres erfahren Sie hier:
16

17 Sie haben als betroffene Person folgende Rechte, **sofern diese Rechte nicht voraussichtlich die**
18 **Verwirklichung des Forschungszwecks unmöglich machen oder ernsthaft beeinträchtigen und**
19 **die Beschränkung für die Erfüllung der Forschungszwecks notwendig ist:**
20
21

22 1. Recht auf Berichtigung:
23

24 Sie haben das Recht, von dem Verantwortlichen unverzüglich die Berichtigung Sie betreffender
25 unrichtiger personenbezogener Daten zu verlangen. Unter Berücksichtigung der Zwecke der
26 Verarbeitung haben Sie das Recht, die Vervollständigung unvollständiger personenbezogener Daten –
27 auch mittels einer ergänzenden Erklärung – zu verlangen.
28
29

30 2. Recht auf Einschränkung der Verarbeitung:
31

32 Sie haben das Recht, von dem Verantwortlichen die Einschränkung der Verarbeitung zu verlangen,
33 wenn eine der folgenden Voraussetzungen gegeben ist:
34

- 35 a) die Richtigkeit der personenbezogenen Daten wird von Ihnen bestritten. Die Einschränkung der
36 Verarbeitung kann in diesem Fall für eine Dauer verlangt werden, die es dem Verantwortlichen
37 ermöglicht, die Richtigkeit der personenbezogenen Daten zu überprüfen;
38 b) die Verarbeitung unrechtmäßig ist und Sie die Löschung der personenbezogenen Daten
39 ablehnen und stattdessen die Einschränkung der Nutzung der personenbezogenen Daten
40 verlangen;
41 c) der Verantwortliche die personenbezogenen Daten für die Zwecke der Verarbeitung nicht
42 länger benötigt, Sie sie jedoch zur Geltendmachung, Ausübung oder Verteidigung von
43 Rechtsansprüchen benötigen
44
45

46 Wurde die Verarbeitung eingeschränkt, so dürfen diese personenbezogenen Daten – von ihrer
47 Speicherung abgesehen – nur mit Ihrer Einwilligung oder zur Geltendmachung, Ausübung oder
48 Verteidigung von Rechtsansprüchen oder zum Schutz der Rechte einer anderen natürlichen oder
49 juristischen Person oder aus Gründen eines wichtigen öffentlichen Interesses der Union oder eines
50 Mitgliedstaats verarbeitet werden.
51
52

53 Haben Sie eine Einschränkung der Verarbeitung erwirkt, werden Sie von dem Verantwortlichen
54 unterrichtet, bevor die Einschränkung aufgehoben wird.
55
56

3. Auskunftsrechte:

Sie haben das Recht, von dem Verantwortlichen eine Bestätigung darüber zu verlangen, ob Sie betreffende personenbezogene Daten verarbeitet werden; ist dies der Fall, so haben Sie ein Recht auf Auskunft über diese personenbezogenen Daten und auf folgende Informationen:

- a) die Verarbeitungszwecke;
 - b) die Kategorien personenbezogener Daten, die verarbeitet werden;
 - c) die Empfänger oder Kategorien von Empfängern, gegenüber denen die personenbezogenen Daten offengelegt worden sind oder noch offengelegt werden, insbesondere bei Empfängern in Drittländern oder bei internationalen Organisationen;
 - d) falls möglich die geplante Dauer, für die die personenbezogenen Daten gespeichert werden, oder, falls dies nicht möglich ist, die Kriterien für die Festlegung dieser Dauer;
 - e) das Bestehen eines Beschwerderechts bei einer Aufsichtsbehörde;
 - f) Sie haben das Recht, vom Verantwortlichen eine Kopie der personenbezogenen Daten, die Gegenstand der Verarbeitung sind, zu erhalten. Für alle weiteren Kopien, die Sie beantragen, kann der Verantwortliche ein angemessenes Entgelt auf der Grundlage der Verwaltungskosten verlangen. Stellen Sie den Antrag elektronisch, so sind die Informationen in einem gängigen elektronischen Format zur Verfügung zu stellen, sofern Sie nichts Anderes angeben.

Das Recht auf Erhalt einer Kopie darf die Rechte und Freiheiten anderer Personen nicht beeinträchtigen.

Die Auskunftsrechte gem. 3. bestehen nicht, wenn die Daten für Zwecke der wissenschaftlichen Forschung erforderlich sind und die Auskunftserteilung einen unverhältnismäßigen Aufwand erfordern würde.

Datum Name der Probandin / des Probanden bzw.
der Patientin/ des Patienten Unterschrift

1
2
3 **Declaration of Consent**
4
5
6
7

8 I hereby confirm that I
9
10
11

12 Ms/Mrs/Mr., born on.....
13
14
15
16

17 would like to participate in the research project „Adherence and psychological health after
18 renal and heart transplantation“ (APT-Study) of the Department of Psychosomatic Medicine
19 and Psychotherapy and the Department of Cardiac Surgery of the University Hospital in
20 Erlangen.
21
22

23 I have read the „Information on study participation“ and agree with the contents and
24 procedures described in this document.
25
26

27 I agree that the aforementioned person/staff member of the above mentioned institution has
28 access to my original medical records.
29
30

31 I agree that all data regarding my person (especially medical data from my medical records)
32 are saved and processed in an encrypted form under the responsibility of the above
33 mentioned institution for the above mentioned study with its respective research questions.
34
35

36 **Withdrawal of consent to data usage**
37
38

39 I know that I can withdraw my consent to data usage by the aforementioned
40 institution/person at any time without giving reasons and that this has no influence on my
41 subsequent medical treatment. In case of withdrawal I agree that my data will continue to be
42 saved for control purposes. However, I have the right to demand its deletion, provided that
43 legal requirements are not opposed to such action. Until withdrawal, the data processing
44 remains legal. I am aware that in case of anonymized storage of my data, deletion is not
45 possible if requested.
46
47
48
49

1
2 **Notes on data security:**
3
4
5

6 **A. General Notes:**
7
8 a. Name and contact data of the person in charge

9 Conduction of the study:
10

11 Dipl.-Psych. Marietta Lieb

12 Department of Psychosomatic Medicine and Psychotherapy

13 Schwabachanlage 6, 91054 Erlangen

14 Phone: 09131-85-45930

15 E-Mail: marietta.lieb@uk-erlangen.de

16
17 Principal Investigator:
18

19 Prof. Dr. (TR) Yesim Erim

20 Department of Psychosomatic Medicine and Psychotherapy

21 Schwabachanlage 6, 91054 Erlangen

22 Phone: 09131-85-35928, Fax: 09131-85-35952

23 E-Mail: yesim.erim@uk-erlangen.de

24 b. Contact data of the data protection officer

25 Dr. Manfred Brunner

26 Phone: 09131-85-46810, Fax: 09131-85-36783

27 E-Mail: manfred.brunner@uk-erlangen.de

28 c. Legal Basis of data processing: Your Consent

29 d. Duration of storage: According to the legally required storage duration for clinical studies

30 e. Right of appeal: You can contact the Bavarian state representative for data security (BayLfD) as
31 supervisory authority, if you opine that the processing of your personal data is illegal:

32 Bavarian state representative for data security (BayLfD)

33 Prof. Dr. Thomas Petri

34 Wagmüllerstraße 18, 80538 Munich

35 Phone: 089 212672-0, E-Mail: Poststelle@datenschutz-bayern.de

36 **B. General rights:**

37 The right to deletion is limited, if your data are required for scientific research.

38 Here you can find further information:

39 1. Right to deletion:

40 Your have the right to request the immediate deletion of personal data and the person in charge is
41 obliged to immediately delete personal data if one of the following reasons applies:

- 42 a) The personal data are no longer necessary for purposes for which they were collected or
43 processed.
- 44 b) You withdraw your consent on which the processing is based and it lacks another legal basis
45 for processing,
- 46 c) The personal data were processed illegitimately.

You have no entitlement to deletion, if your data are necessary for scientific research and the deletion prevents or seriously affects the aims of processing. Or the processing is required for the assertion, exercise, or defense of legal rights

2. Disclosure requirements in the context of correction or deletion of personal data or the restriction of processing:

The person in charge informs all recipients, who have received personal data, about each correction or deletion of personal data or the restriction of processing, unless it proves impossible or is associated with a disproportionate effort. The person in charge informs you about those recipients upon request.

The right to data transfer is restricted or excluded, if the research is on the public's behalf or the data constitute a business secret.

Here you can find further information:

3. The right to data transfer:

- a) You have the right to receive your personal data that you provided a person in charge, in a structured, common, machine-readable format, and you have the right to transmit these data to another person in charge without hindrance by the person in charge who these data were provided to, if the processing is done by means of an automated process.
- b) In the exercise of your right to data transfer according to section a) you have the right to obtain that the personal data are directly transferred from one person in charge to another, if it is technically feasible.
- c) The exercise of your right to data transfer does not affect the right to deletion of data. This right does not apply for processing that is required for the performance of a task assigned to the person in charge that is on the public's behalf or is done with the exercise of official authority.
- d) The right according to section 2 must not affect the rights and freedoms of other persons.

Notes:

in case of mere academic research:

Research conducted during this study is not on the behalf of the public. Therefore the right to data transfer cannot be exercised.

If personal data are transferred to a third country or an international organization, you have the right to be informed about the adequate security in association with the transfer according to the article 46 DSGVO.

C. **Rights that are restricted by the research purpose:**

The right to correction, restriction of processing and disclosure are excluded, if these rights prevent or seriously affect the expected research purpose and the restriction is necessary for the completion of the research purpose.

Here you can find further information:

1
2
3 As a person concerned you have the following rights, if these rights presumably do not prevent or
4 seriously affect the realization of the research purpose and the restriction is necessary for the completion
5 of the research purpose:
6
7

8 1. Right to correction:
9

10 You have the right to demand an immediate correction of incorrect personal data from the person in
11 charge. In consideration of the purposes of processing you have the right to demand the completion of
12 incomplete personal data – also by means of an additional explanation.
13
14

15 2. Right to restriction of processing:
16

17 You have the right to demand the restriction of processing, if one of the following conditions is given:
18

- 19 a) The correctness of the personal data is denied. In this case the restriction of processing can be
20 demanded for a duration that enables the person in charge to verify the correctness of personal
21 data;
22 b) the processing is illegitimate and you decline the deletion of personal data and instead you demand
23 the restriction of usage of personal data
24 c) the person in charge does no longer need the personal data for the purposes of processing,
25 although you need them for assertion, exercise or defense of legal rights.
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27

28 If the processing is restricted, – except for their storage - the personal data can only be processed with
29 your consent or for the assertion, exercise or defense of legal rights or for the protection of the rights of
30 other natural or juridical persons or for reasons of an important public interest of the Union or other
31 member states.
32

33 If you have obtained the restriction of processing, you will be informed by the person in charge before the
34 restriction is being cancelled.
35
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37 3. Disclosure rights:
38

39 You have the right to obtain a confirmation from the person in charge on whether the personal data are
40 being processed; in this case you have the right to disclosure about these personal data and the
41 following information:
42

- 43 a) Purposes of processing;
44 b) The categories of personal data that are processed;
45 c) The recipients or categories of recipients who the personal data were or will be disclosed to,
46 especially the recipients in third countries or international organizations;
47 d) If possible, the expected duration of the storage of personal data, or if possible, the criteria for the
48 determination of the duration
49 e) The existence of a right of appeal to a supervisory authority.
50 f) You have the right to receive a copy of the personal data that are subject of processing from the
51 person in charge. For all further copies that you request, the person in charge can claim an
52 adequate fee on the basis of the administrative expenses. If you file the application electronically,
53 the information are to be provided in a usual electronic format, unless you do not indicate anything
54 else.
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57 The right to the receipt of a copy must not affect the rights and freedoms of other persons.
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3 The disclosure rights according to 3 do not apply, if the data are required for purposes of scientific
4 research and the provision of information requires disproportionate effort.
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10 Date

11 Name of participant

12 Signature

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For peer review only

1 Attachment File 2: Study information as received by the patient (German and English)
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Information zur Studienteilnahme

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9 **Sehr geehrte Interessentin, sehr geehrter Interessent,**
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11

12 die psychosomatische und psychotherapeutische Abteilung des Universitätsklinikums
13 Erlangen führt in Kooperation mit der Herzchirurgischen Klinik im Rahmen der
14 Transplantationsnachsorge eine Studie mit dem Titel „**Adhärenz und psychische**
15 **Gesundheit nach Nieren- und Herztransplantation“ (APT-Studie)** durch.
16
17

18 **Ziel der Studie ist es**, mithilfe einer elektronischen Pillenbox die regelmäßige Einnahme
19 (Adhärenz) der verschriebenen Immunsuppressiva zu überwachen, mit Ihrer
20 Selbsteinschätzung zu vergleichen, sowie mit psychologischen Faktoren in Verbindung zu
21 bringen. **Wie Sie wissen ist die regelmäßige Einnahme der Immunsuppressiva nach der**
22 **Transplantation ein für den Organerhalt immens wichtiger Beitrag von Ihnen.** Die
23 Studie zielt darauf ab, diese regelmäßige Einnahme zu untersuchen und zu verbessern.
24 Es ergeben sich keine Änderungen hinsichtlich Ihrer gewöhnlichen Nachsorgebehandlung
25 und die Studie ist mit keinerlei Risiken oder Kosten verbunden.
26
27

28 **Ablauf und Inhalte der Studie:**
29
30

31 Zunächst möchten wir Sie bitten die mitgesendeten Fragebögen zu beantworten und wenn
32 möglich bei Ihrem Termin zur Nachsorgeuntersuchung ausgefüllt mitzubringen.
33
34

35 **Während eines ersten persönlichen Termins (ca. 15-20 Minuten)**, direkt nach Ihrer
36 Untersuchung, erfolgt die **Ausgabe der elektronischen Pillenbox**. Dieses Gerät ist in
37 Deutschland zugelassen und wurde von uns in einer Vorstudie bezüglich der technischen
38 Eigenschaften überprüft. Zudem wurde das Gerät vom Datenbeauftragten des
39 Universitätsklinikums als unbedenklich eingeschätzt. Es erfolgt eine ausführliche Erklärung
40 und Demonstration der einfachen und benutzerfreundlichen Handhabung.
41
42

43 In einem **dreimonatigen Zeitraum** werden Sie **von zuhause aus** die Pillenbox anwenden,
44 während die Einnahme der Medikation automatisch aufgezeichnet wird. Es werden
45 **zweiwöchentlich Telefonate** (ca. 5 Minuten) stattfinden, während welcher sie vier Fragen
46 zu Ihrer Medikamenteneinnahme beantworten.
47
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49 **Nach 3 Monaten** gibt es, wenn gewünscht, einen **weiteren persönlichen Termin**, während
50 dessen Sie ein **ausführliches Feedback** über Ihre Medikamenteneinnahme (Adhärenz)
51 erhalten, sowie die Pillenbox abgeben. Falls ein persönlicher Termin nicht möglich ist, kann
52 die Box gerne auch auf dem Postweg zurückgegeben werden. Die Rückmeldung wäre in
53 diesem Fall auch telefonisch möglich.
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2 **Informationen zum Datenschutz:**
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4 Alle erhobenen Daten werden in **vollständig verschlüsselter Form** elektronisch
5 abgespeichert und nur zu Forschungszwecken verwendet. Jeder Teilnehmer erhält einen
6 **Probandencode**, welcher es erlaubt, die personenbezogenen Daten in pseudonymisierter
7 Form zusammenzuführen. Außenstehende können keinen Zusammenhang zwischen den
8 Daten und Ihrer Person herstellen. Nur die für die Studie verantwortlichen Personen haben
9 Zugang zu Ihren persönlichen Daten.
10
11

12 **Einwilligung zur Teilnahme und Widerrufsrecht:**
13

14 Ihre Teilnahme an der Untersuchung ist freiwillig und bedarf Ihrer datenschutzrechtlichen
15 Einwilligung (siehe Beiblatt „Datenschutzrechtliche Einwilligungserklärung“). Die einmalig
16 gegebene Zustimmung zur Studienteilnahme können Sie jederzeit ohne Angabe von
17 Gründen widerrufen, ohne dass Sie Nachteile für Ihre weitere medizinische Versorgung am
18 Universitätsklinikum Erlangen befürchten müssen.
19
20

21 Bei Fragen zur Studie steht Ihnen unsere Projektmitarbeiterin **Frau Dipl. Psych. Marietta**
22 **Lieb (Tel.: 09131-8545930; Email: marietta.lieb@uk-erlangen.de)** gerne zur Verfügung.
23
24

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26
27 *Wir würden uns über Ihre Studienteilnahme sehr freuen und danken Ihnen im Voraus*
28 *recht herzlich für Ihre Unterstützung!*
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Information on study participation

Dear Reader,

the Department of Psychosomatic Medicine and Psychotherapy of the University Hospital in Erlangen is conducting a study titled „**Adherence and psychological health after renal and heart transplantation“ (APT-Study)** in cooperation with the Department of Cardiac Surgery.

The aim of this study is to survey the regular intake (adherence) of your prescribed immunosuppressive medication with the aid of an electronic pillbox. We wish to compare these results with your self-assessment and to make a connection with a variety of psychosocial factors.

As you are aware, the regular intake of your immunosuppressants is a vital contribution for organ survival. The study aims to examine and to improve this regular intake. Study participation does not result in any changes in respect to your usual follow-up examinations and does not involve any costs or risks.

Study procedure and contents:

Initially, we would like to ask you to fill-in the enclosed questionnaires and to bring them along to your next follow-up examination.

During the first personal appointment (app. 15-20 minutes), directly after your examination, the **handover of the pillbox will take place.** The device is approved in Germany and was tested with respect to its technical features in a pre-study. Further, the device was classified as safe by the data protection officer of the University Hospital. A detailed explanation and demonstration of the simple and user-friendly handling of the device will take place.

During a 3 months period, you will use the pillbox **from your home.** Meanwhile the medication intake will be registered automatically. **In an interval of two weeks,** phone calls of app. 5 minutes will take place during which you will receive four questions on your medication intake.

After 3 months, a second appointment will take place during which you will receive a **detailed feedback** (optional) on your medication intake (adherence) and hand over your pillbox. If a personal appointment is not feasible, the pillbox can also be returned by mail. In this case, the feedback can also be given via phone.

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2 **Information on data security:**
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4 All collected data are **encoded**, saved electronically, and are only used for research
5 purposes. Each participant receives a code, which allows the merging of personal data in
6 pseudomized form. External parties are not able to establish a link between the data and
7 your person. Only the person responsible for the study has access to your data.
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11 **Consent to participation and right of withdrawal**
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13 Participation is voluntary and requires a declaration of consent (please see supplement
14 „Declaration of Consent“). It is possible to withdraw the consent to participation at any given
15 time without giving reasons. A withdrawal will not entail any disadvantages for your
16 subsequent medical treatment at the University Hospital Erlangen.
17
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19
20 If you have further questions on the study, the project assistant **Ms. Dipl-Psych. Marietta**
21 **Lieb** will be at your disposal (phone: 09131-8545930, E-Mail: marietta.lieb@uk-erlangen.de).
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25 We would appreciate your participation and thank you very much in advance for your
26 support!
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Attachment File 3: Graded target levels of the different immunosuppressive regimens

Immunosuppressive Medication	Time since transplantation	Target Level
Prograf/Advagraf®	< 6 months	12-15ng/ml
	7-12 months	10-15ng/ml
	> 12 months	7-10ng/ml
Sandimmun®	< 6months	250-350ng/ml
	6-12 months	200-250ng/ml
	>12 months	150-200ng/ml
Certican®	-----	3-8 µg/l
Prograf® + Certican®		
Prograf®	< 12 months	8-10ng/ml
	>12 months	6-7ng/ml
Certican®	-----	4-7 µg/l
Sandimmun® + Certican®		
Sandimmun®	-----	100-120ng/ml
Certican®	-----	3-8 µg/l